

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

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
	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 <u>licence</u>.

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 <u>Creative Commons</u> 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.

R. O.

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:

- <u>corresponding author</u> Mrs. Ravina Barrett (<u>https://orcid.org/0000-0003-0004-</u> 2131) MPharm, FHEA, MSc Finance, Author affiliations and information:
 - Senior Lecturer in Pharmacy Practice, School of Pharmacy and Biomolecular Sciences, Cockcroft Building, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ. +44(0)1273643986, <u>R.Barrett2@Brighton.ac.uk</u>
 - 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, <u>ravina.barrett@port.ac.uk</u>.
- 2. Mr. Robert Barrett, MBA, MCSE, MCSA, MCP, ITIL, Prince 2 <u>rob-barrett@outlook.com</u>; <u>https://orcid.org/0000-0003-3402-3377</u> 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, <u>X.Lin@soton.ac.uk</u>
- 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, <u>d.j.culliford@soton.ac.uk</u>
- 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 (<u>https://orcid.org/</u>) <u>S.Fraser@soton.ac.uk</u>.
- 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, <u>cedwards@soton.ac.uk</u>

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 twotailed 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.

or oper terier only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

3 4

5

6 7

8 9

10

11 12

13

14

15

16

17

18 19

20

21

22

23 24

25

26

27

28

29 30

31

32

33

34

35

36

37 38

39

40 41

42

43

44 45

46

47

48

49

50

51

52

53

54 55

56

57 58

59

60

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 trends¹⁷ 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 Checklist¹⁸ 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 Qu	antity	Actual C	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 antirheumatics 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)	Parameter	Standard	t-statistic	p-value	Lower Cl	Upper Cl
BEFORE March 2020	Estimate	Error				
Sulfasalazine-Model_1	5435	27256	0.199	0.844	-51247.9	62118.12
Hydroxychloroquine sulfate-	-10955	14016	-0.782	0.445	-40102.8	18192.08
Model_2 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	Standard	t	p-value		
	Estimate	Error				
Sulfasalazine-Model_1	2179999	1138801	1.914	0.072	-188267	4548266
Hydroxychloroquine sulfate-	1411431	585611	2.41	<u>0.027</u>	193586	2629275
Model_2						
Azathioprine-Model_3	1284202	494659	2.596	<u>0.018</u>	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	Parameter	Standard	t	p-value		
February 2020	Estimate	Error				
Sulfasalazine-Model_1	-131622	69041	-1.906	0.073	-275201	11957.49
Hydroxychloroquine sulfate-	-61802	35503	-1.741	0.099	-135635	12031.47
Model_2						
Azathioprine-Model_3	-63144	29989	-2.106	<u>0.050</u>	-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 <u>https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd</u> 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.

- 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_documentsupply_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).
- 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.

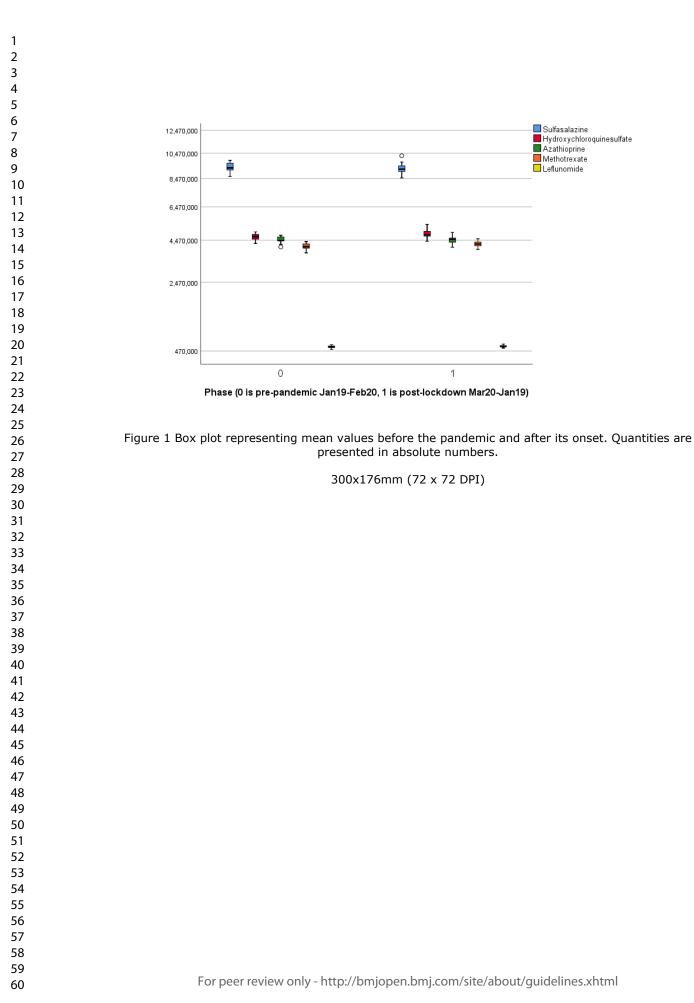
- 19. Without more nurses, NHS 111 staff could be 'overwhelmed'. Emerg Nurse 2015; 23: 6–6.
- 20. Osamor K. I warned parliament that NHS 111 would never be able to cope. *The Guardian*, 23 April 2020, https://www.theguardian.com/commentisfree/2020/apr/23/nhs-111-crisis-coronavirus-pandemic (23 April 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.

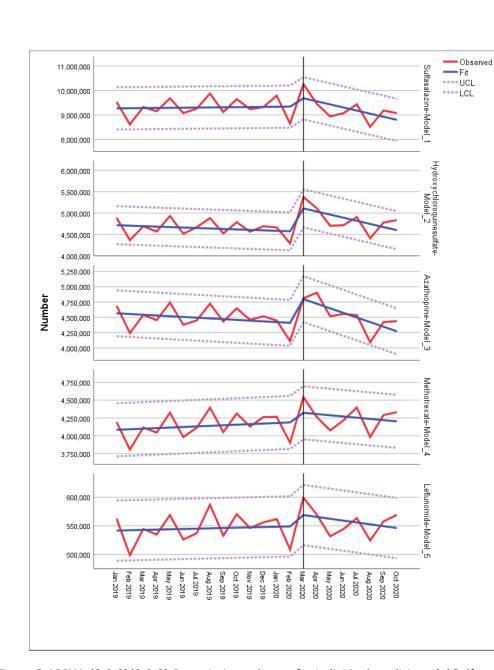
Figure 1 Box plot representing mean values before the pandemic and after its onset. Quantities are presented in absolute numbers.

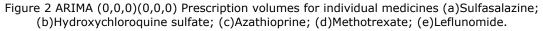
Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

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).





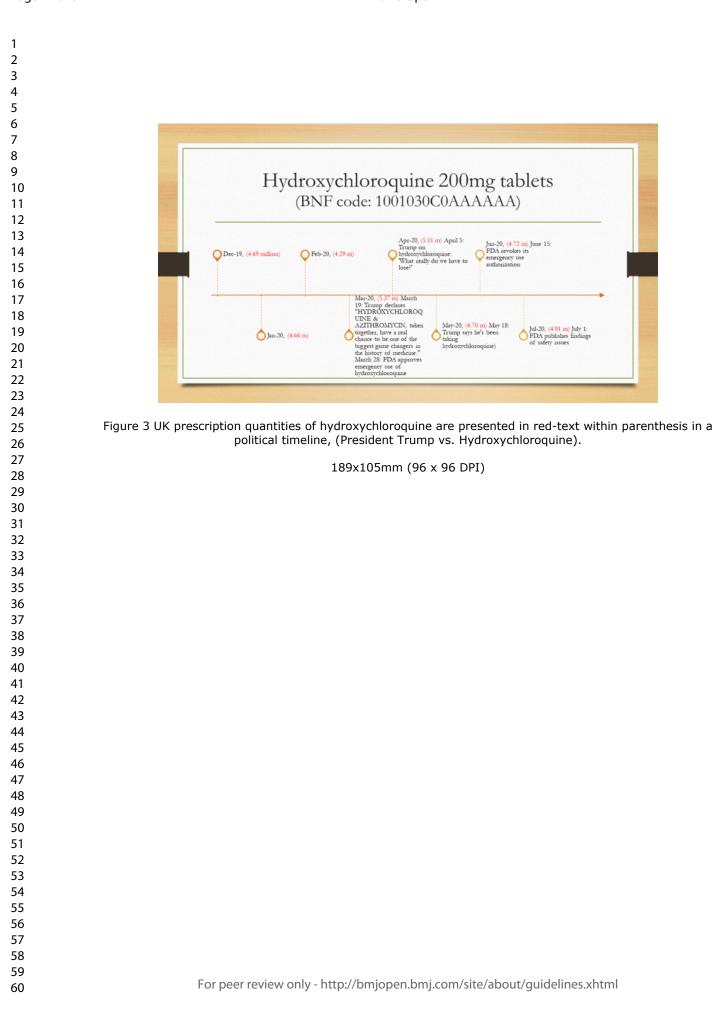


272x347mm (72 x 72 DPI)

Jun-20, (4.72 m) June 15: FDA revokes its

Jul-20, (4.91 m) July 1: FDA publishes finding of safety issues

emergency use authorization



BMJ Open: first published as 10.1136/bmjopen-2021-051936 on 23 December 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

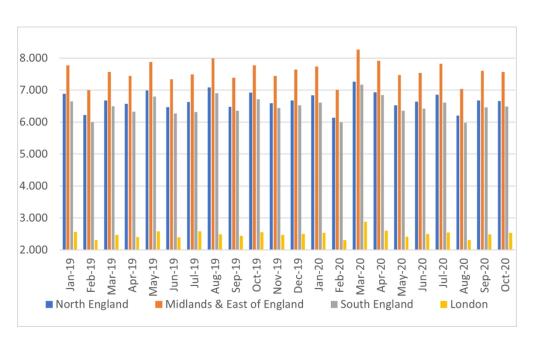


Figure 4 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

127x76mm (300 x 300 DPI)

Page 19 of 32 Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21

2	
3	* Encoding: UTF-8.
4	
5	
6	DATASET ACTIVATE DataSet3.
7	PREDICT THRU END.
8	* Time Series Modeler.
9	TSMODEL
10	/MODELSUMMARY PRINT=[MODELFIT]
11	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
12	/MODELDETAILS PRINT=[PARAMETERS]
13	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
14	
15	
16	/SAVE PREDICTED(Predicted) LCL(LCL) UCL(UCL)
17	AUXILIARY CILEVEL=95 MAXACFLAGS=24
18	/MISSING USERMISSING=EXCLUDE
19	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
20	e
21	INDEPENDENT=TimePeriod Phase Interact
22	PREFIX='Model'
23	ARIMA AR=[1] DIFF=0 MA=[0]
24	TRANSFORM=NONE CONSTANT=YES
25	
26	/AUTOOUTLIER DETECT=OFF.
27	
28	PREDICT THRU END.
29	* Time Series Modeler.
30 31	TSMODEL
32	/MODELSUMMARY PRINT=[MODELFIT]
32 33	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
33 34	/MODELDETAILS PRINT=[PARAMETERS]
34 35	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
36	
37	
38	/SAVE PREDICTED(Predicted) LCL(LCL) UCL(UCL)
39	/AUXILIARY CILEVEL=95 MAXACFLAGS=24
40	/MISSING USERMISSING=EXCLUDE
41	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
42	e
43	INDEPENDENT=TimePeriod Phase Interact
44	PREFIX='Model'
45	/ARIMA AR=[0] DIFF=1 MA=[0]
46	TRANSFORM=NONE CONSTANT=YES
47	
48	/AUTOOUTLIER DETECT=OFF.
49	
50	PREDICT THRU END.
51	* Time Series Modeler.
52	TSMODEL
53	/MODELSUMMARY PRINT=[MODELFIT]
54	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
55	/MODELDETAILS PRINT=[PARAMETERS]
56	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
57	/OUTPUTFILTER DISPLAY=ALLMODELS
58	AUXILIARY CILEVEL=95 MAXACFLAGS=24
59	
60	/MISSING USERMISSING=EXCLUDE

2	
3	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
4	e
5	INDEPENDENT=TimePeriod Phase Interact
6	
7	PREFIX='Model'
8	/ARIMA AR=[0] DIFF=0 MA=[1]
9	TRANSFORM=NONE CONSTANT=YES
10	/AUTOOUTLIER DETECT=OFF.
11	
12	PREDICT THRU END.
13	* Time Series Modeler.
14	
15	TSMODEL
16	/MODELSUMMARY PRINT=[MODELFIT]
17	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
18	/MODELDETAILS PRINT=[PARAMETERS]
19	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
20	/OUTPUTFILTER DISPLAY=ALLMODELS
21	AUXILIARY CILEVEL=95 MAXACFLAGS=24
22	
23	/MISSING USERMISSING=EXCLUDE
24	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
25	e
26	INDEPENDENT=TimePeriod Phase Interact
27	PREFIX='Model'
28	/ARIMA AR=[0] DIFF=0 MA=[0]
29	TRANSFORM=LN CONSTANT=YES
30	TRANSFORM-LIN CONSTANT-TES
31	/AUTOOUTLIER DETECT=OFF.
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
52	
55	
55	
55	
57	
57	
50	
59 60	
59 60	

Page 21 of 32 BMJ Open Supplementary Table 2 - Sensitivity analysis (Mar20-1) Jan 19 to Jan 21

ARIMA(0,0,0), No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Error	T-stat	P-value	ARIMA(0,0,0) Natural Logarithm, No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Para Estir
Sulfasalazine-Model_1	TimePeriod	5435	28871	0.188	0.852	Sulfasalazine-Model_1	TimePeriod	
Sulfasalazine-Model_1	Phase	659017	875894	0.752	0.46	Sulfasalazine-Model_1	Phase	
Sulfasalazine-Model_1	Interact	-38151	50570	-0.754	0.459	Sulfasalazine-Model_1	Interact	
Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955	14336	-0.764	0.453	Hydroxychloroquinesulfate-Model_2	TimePeriod	
Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	814729 -24392	434936 25111	1.873 -0.971	0.075 0.342	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	
Azathioprine-Model_3	TimePeriod	-12052	12273	-0.982	0.337	Azathioprine-Model 3	TimePeriod	
Azathioprine-Model_3	Phase	786705	372342	2.113	0.047	Azathioprine-Model_3	Phase	
Azathioprine-Model_3	Interact	-31340	21497	-1.458	0.16	Azathioprine-Model_3	Interact	
Methotrexate-Model_4	TimePeriod	7966	11836	0.673	0.508	Methotrexate-Model_4	TimePeriod	
Methotrexate-Model_4 Methotrexate-Model_4	Phase	249614 -10634	359099 20733	0.695 -0.513	0.495	Methotrevate-Model_4	Phase Interact	
_eflunomide-Model_5	Interact TimePeriod	561	1662	0.313	0.739	Methotrexate-Model_4 Leflunomide-Model_5	TimePeriod	
_eflunomide-Model_5	Phase	30388	50436	0.603	0.553	Leflunomide-Model_5	Phase	
_eflunomide-Model_5	Interact	-1188	2912	-0.408	0.687	Leflunomide-Model_5	Interact	
	TimePeriod (Before); Phase	Parameter						
ARIMA(1,0,0), AR	(Step); Interact (After)	Estimate	Standard Erro		P-value		6	
Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod	19759	20233	0.977	0.34	the coefficient for 'time' gives us the slop		vention
Sulfasalazine-Model_1	Phase Interact	417103 -37930	614888 34973	0.678	0.505	the coefficient for 'phase' gives us the ch the coefficient for 'interact' gives us the		rventio
Hydroxychloroquinesulfate-Model_2	TimePeriod	-5175	11041	-0.469	0.644	the coefficient for interact gives us the	enange in slope pre and post inte	i venuo
Hydroxychloroquinesulfate-Model_2	Phase	700712	335790	2.087	0.05	If the coefficient for time is β 1, for phase	e is β2 and for interact is β3 then t	the regr
Hydroxychloroquinesulfate-Model_2	Interact	-23233	19100	-1.216	0.238			
Azathioprine-Model_3	TimePeriod	-9123	10465	-0.872	0.394	Therefore, pre intervention becomes:		
Azathioprine-Model_3	Phase	738472	317473	2.326	0.031	Outrouve and the Otto		
Azathioprine-Model_3 Methotrexate-Model_4	Interact TimePeriod	-31213 14064	18041 7165	-1.73 1.963	0.099	Outcome = constant + β 1time		
Methotrexate-Model_4	Phase	86932	218834	0.397	0.695	Outcome= constant + β1time + β2 + β3in	teract = (constant + B2) + (B1 + B	3) time
 Methotrexate-Model_4	Interact	-7128	12399	-0.575	0.572	(as time and interact are the same post i		.,
	TimePeriod	1432	1106	1.295	0.21			
eflunomide-Model_5 eflunomide-Model_5 eflunomide-Model_5	Phase	11071	33718	0.328	0.746			
eflunomide-Model_5	Interact	-882	1912	-0.461	0.649			
	The Desired (D. C. J. D.	Dama i						
ARIMA(0,1,0), Difference	TimePeriod (Before); Phase (Step); Interact (After)	Parameter Estimate	Standard Erro	T-stat	P-value	Total Quantities		
ARIMA(0,1,0), Difference Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod	Estimate -16503	54217	-0.304	0.764	Total Quantities 11 months after this date (Mar-20 to Jan	21) .	
Sulfasalazine-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase	Estimate -16503 446642	54217 1491083	-0.304 0.3	0.764		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase Interact	Estimate -16503 446642 -5626	54217 1491083 88335	-0.304 0.3 -0.064	0.764 0.768 0.95		21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2	(Step); Interact (After) TimePeriod Phase Interact TimePeriod	Estimate -16503 446642 -5626 -4262	54217 1491083 88335 29227	-0.304 0.3 -0.064 -0.146	0.764 0.768 0.95 0.886		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase	Estimate -16503 446642 -5626 -4262 712710	54217 1491083 88335 29227 803796	-0.304 0.3 -0.064 -0.146 0.887	0.764 0.768 0.95 0.886 0.386		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2	(Step); Interact (After) TimePeriod Phase Interact TimePeriod	Estimate -16503 446642 -5626 -4262	54217 1491083 88335 29227	-0.304 0.3 -0.064 -0.146	0.764 0.768 0.95 0.886		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact	Estimate -16503 446642 -5626 -4262 712710 -29016	54217 1491083 88335 29227 803796 47618	-0.304 0.3 -0.064 -0.146 0.887 -0.609	0.764 0.768 0.95 0.886 0.386 0.549		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 +ydroxychloroquinesulfate-Model_2 +ydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact	Estimate -16503 446642 -5626 -4262 712710 -29016 -6734 573262 -21531	54217 1491083 88335 29227 803796 47618 23232 638927 37851	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569	0.764 0.768 0.95 0.886 0.386 0.549 0.775 0.38 0.576		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Ulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod TimePeriod	Estimate -16503 446642 -5626 -4262 712710 -29016 -6734 573262 -21531 -6809	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292	0.764 0.768 0.95 0.886 0.386 0.549 0.775 0.38 0.576 0.773		-21).	
sulfasalazine-Model_1 sulfasalazine-Model_1 Julfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Wethotrexate-Model_4	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase	Estimate -16503 446642 -5626 -4262 712710 -29016 -6734 573262 -21531 -6809 439338	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685	0.764 0.768 0.95 0.886 0.386 0.549 0.775 0.38 0.576 0.773 0.501		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Ulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact	Estimate -16503 446642 -5626 -4262 712710 -29016 -6734 573262 -21531 -6809 439338 -15532	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409	0.764 0.768 0.95 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Wethotrexate-Model_4	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase	Estimate -16503 446642 -5626 -4262 712710 -29016 -6734 573262 -21531 -6809 439338	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685	0.764 0.768 0.95 0.886 0.386 0.549 0.775 0.38 0.576 0.773 0.501		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Methotrexate-Model_4	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod TimePeriod	Estimate -16503 -46642 -5626 -4262 712710 -29016 -6734 573262 -21531 -6809 439338 -15532 -753	54217 1491083 88335 29227 803796 47618 23232 638927 37851 2305 640948 37971 3188	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236	0.764 0.768 0.95 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816		-21).	
sulfasalazine-Model_1 sulfasalazine-Model_1 Julfasalazine-Model_1 +ydroxychloroquinesulfate-Model_2 +ydroxychloroquinesulfate-Model_2 +ydroxychloroquinesulfate-Model_2 +ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Leflunomide-Model_5 .eflunomide-Model_5	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase	Estimate -16503 446642 -5626 -4262 712710 -6734 573262 -21531 -6809 439338 -15532 -753 58732	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971 3188 87689	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67	0.764 0.768 0.95 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Jydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase	Estimate -16503 446642 -5626 -4262 712710 -6734 573262 -21531 -6809 439338 -15532 -753 58732	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971 3188 87689	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67	0.764 0.768 0.95 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511		-21).	
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Jydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase (Step); Phase (Step); Interact (After)	Estimate - 16503 446642 - 5626 - 4262 712710 - 6734 573262 - 21531 - 6809 439338 - 15532 - 753 58732 - 2093 - 2093 - 2093 - 2094 - 2005 - 2	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971 3188 87689 5195 5195	-0.304 0.3 -0.064 0.146 0.887 -0.609 -0.292 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67 -0.403	0.764 0.768 0.95 0.886 0.386 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.681 0.511	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Jydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Methotrexate-Model_4 Methotrexate-Model_4 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5	(Step): Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before); Phase (Step): Interact (After) TimePeriod	Estimate - 16503 446642 - 5626 - 4262 712710 - 29016 - 6734 573262 - 21531 - 6809 439338 - 15532 - 7533 58732 - 2093 - 2094 - 2095 -	54217 1491083 88335 29227 803796 47618 23305 640948 37971 3188 87689 5195 5 5	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.685 -0.409 -0.292 0.685 -0.409 -0.236 -0.403 -0.236 -0.403 -0.236 -0.403 -0.403 -0.403 -0.403 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.405 -0.404 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0.405 -0	0.764 0.768 0.955 0.886 0.386 0.775 0.38 0.775 0.38 0.773 0.501 0.687 0.511 0.691 P-value 0.011	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Methotrexate-Model_4 Methotrexate-Model_4 Sulfasalazine-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before); Phase (Step); Interact (After) TimePeriod Phase	Estimate - 16503 - 46642 - 5626 - 4262 - 712710 - 29016 - 6734 - 6309 - 43938 - 15532 - 7533 - 7535 - 7535 - 7535 - 7535 - 7555 - 755	54217 1491083 88335 29227 803796 47618 23325 23305 63927 37885 23305 640948 37971 3188 87689 5195 5195 5195 51964 5195 51964 5195 5197 5197 5197 5195 5197 5197 5197	-0.304 0.3 -0.064 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67 -0.403 -0.403 -0.403	0.764 0.768 0.955 0.886 0.386 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.691	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interac	Estimate - 16503 446642 - 5626 - 4262 712710 - 6734 573262 - 21531 - 6809 4439338 - 15532 - 753 58732 - 2093 - 2093 - 27834 - 27834 459301 - 50867 - 50867	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.299 -0.299 -0.299 -0.299 -0.299 -0.236 -0.409 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.409 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.405 -0.409 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.236 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.691 P-value 0.218 0.228	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before); Phase (Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod	Estimate - 16503 446642 - 5626 - 4262 712710 - 29016 - 6734 4573262 - 21531 - 6809 439338 - 15532 - 7533 - 58732 - 2093 - 2094 - 2094 - 2094 - 2095 - 2095	54217 1491083 88335 29227 803796 47618 22322 638927 37851 23305 640948 37971 3188 87689 5195 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67 -0.403 -0.238 1.091 -2.361 -2.388 1.091 -2.361 0.223	0.764 0.768 0.955 0.886 0.349 0.775 0.38 0.773 0.501 0.687 0.511 0.691 P-value 0.011 0.288 0.228 0.826	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Methotrexate-Model_4 Methotrexate-Model_4 Sulfasalazine-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interac	Estimate - 16503 446642 - 5626 - 4262 712710 - 6734 573262 - 21531 - 6809 4439338 - 15532 - 753 58732 - 2093 - 2093 - 27834 - 27834 459301 - 50867 - 50867	54217 1491083 88335 29227 803796 47618 23232 638927 37851 23305 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.299 -0.299 -0.299 -0.299 -0.299 -0.236 -0.409 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.409 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.404 -0.404 -0.404 -0.404 -0.404 -0.404 -0.405 -0.409 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.299 -0.236 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403 -0.403	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.691 P-value 0.218 0.228	11 months after this date (Mar-20 to Jan		
sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_2 vtydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Methotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 Julfasalazine-Model_1 Julfasalazine-Model_1 Julfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2 Sulfasalazine-Model_2	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before); Phase (Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact	Estimate - 16503 - 46642 - 5626 - 4262 - 712710 - 29016 - 6734 - 6309 - 43938 - 15532 - 21531 - 6309 - 43938 - 15532 - 2093 - 7533 - 7535 - 7555 -	54217 1491083 88335 29227 803796 47618 22322 638927 37885 23305 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5196 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21544 21545 21545 21545 21545 21545 21545 21545 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 21555 215555 21555 21555 21555 21555 21555 21555 21555 215555 21555 21555 215555 21555 21555 215555 215555 21555 21555 21555 21555 215555 21555 21555 21555 215555 21555 21555 21555 21555 215555 21555 21555 215555 215555 21555 215555 21555 21555 215555 215555 215555 2155555 215555 215555 2155555 2155555 2155555 2155555 21555555 2155555555	-0.304 0.3 -0.644 -0.146 0.887 -0.299 -0.292 0.685 -0.292 -0.236 0.67 -0.409 -0.236 0.67 -0.403 -0.236 1.07 2.788 1.091 -2.361 0.223 3.065	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.683 0.928 0.228 0.228 0.228 0.228 0.228 0.228	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Authoumide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Julfasalazine-Model_1 Julfasalazine-Model_1 Julfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_2 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_2 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathiop	(Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before); Phase (Step); Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact Interact	Estimate - 16503 - 46642 - 5626 - 4262 - 712710 - 29016 - 6734 - 573262 - 21531 - 6809 - 43938 - 15532 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 75 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 753 - 75 - 75 - 75 - 75 - 75 - 75 - 75 - 75	54217 1491083 88335 29227 803796 47618 22322 638927 37885 23305 639927 37885 87899 5195 5195 5195 5195 5195 5195 5195 5	-0.304 0.3 -0.644 -0.146 0.887 -0.299 -0.292 -0.887 -0.292 -0.292 -0.292 -0.236 -0.409 -0.236 -0.403 -0.403 -0.236 1.091 -2.361 0.223 -2.51 -0.481 3.395	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.288 0.228 0.228 0.228 0.228 0.228 0.228 0.028	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathiop	(Step); Interact (After) TimePeriod Phase Interact TimePeriod (Before); Phase (Step); Interact (After) TimePeriod Phase Interact Interact	Estimate -16503 -46642 -5626 -4262 -712710 -29016 -6734 573262 -21531 -6809 439338 -15532 -753 58732 -2093 -2093 -2093 -2093 -278 4459301 -50867 -1157 -637368 -26929 -2278 660176 -34495	54217 1491083 88335 29227 803796 47618 23305 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.064 -0.146 0.887 -0.299 -0.299 -0.299 -0.299 -0.299 -0.236 -0.409 -0.236 -0.403 -0.403 -0.236 -0.403 -2.511 -0.481 3.065 -2.511 -0.481 3.3873	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.691 0.826 0.001 0.028 0.826 0.001	11 months after this date (Mar-20 to Jan		
Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 4ydroxychloroquinesulfate-Model_2 4ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_1 Sulfasalazine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathiop	(Step): Interact (After) TimePeriod Phase Interact Interact Interact TimePeriod Phase Interact	Estimate - 16503 446642 - 5626 - 4262 712710 - 29016 - 6734 439338 - 15532 - 21531 - 6809 439338 - 15532 - 753 358732 - 2093 - 2094 - 2084 - 20867 - 1157 - 50867 - 2198 - 2092 - 2278 - 600176 - 34495 -	54217 1491083 88335 29227 803796 47618 22322 638927 3785 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.064 -0.146 0.887 -0.609 -0.29 0.897 -0.569 -0.292 0.685 -0.409 -0.236 0.67 -0.236 -0.403 -0.233 -0.67 -0.236 -0.403 -0.233 -0.67 -0.235 -0.67 -0.236 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.235 -0.67 -0.259 -0.235 -0.259 -0.235 -0.259 -0.235 -0.259 -0.235 -0.259 -0.235 -0.259 -0.235 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.235 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.259 -0.255 -0.259 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.255 -0.25	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.773 0.501 0.681 0.511 0.691 0.511 0.691 0.511 0.691 0.511 0.691 0.511 0.636 0.0021 0.636 0.001 0.0001 0.00007	11 months after this date (Mar-20 to Jan		
sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Methotrexate-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_2 xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_3 Xathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4	(Step): Interact (After) TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod Phase Interact TimePeriod (Before): Phase (Step): Interact (After) TimePeriod Phase Interact Interact Interact Interact Interact Interact Interact	Estimate - 16503 - 46642 - 5626 - 4262 - 712710 - 29016 - 6734 - 573262 - 21531 - 6809 - 43938 - 15532 - 753 - 583 - 58732 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 20 - 20 - 20 - 20 - 20 - 20 - 20 - 20	54217 1491083 88335 29227 803796 47618 22322 638927 37885 23305 639927 37885 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.644 -0.146 0.887 -0.299 -0.292 -0.887 -0.292 -0.292 -0.292 -0.236 -0.409 -0.236 -0.403 -0.403 -0.236 -2.51 -0.481 -2.51 -0.481 -3.873 -3.873 -3.873 -0.236	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.288 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.221 0.636 0.001 0.001 0.0001 0.0001 0.0001 0.0001 0.816	11 months after this date (Mar-20 to Jan		
sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 sulfasalazine-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4	(Step): Interact (After) TimePeriod Phase Interact Interact Interact TimePeriod Phase Interact	Estimate -16503 -46642 -5626 -4622 -21531 -6809 439338 -15532 -753 58732 -2093 -2093 -2783 -2093 -2783 -2783 -50867 -1157 -637368 -26929 -22784 -26929 -22784 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -27834 -2783 -2783 -2784 -2783 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -2784 -278 -278 -278 -278 -278 -278 -278 -278	54217 1491083 88335 29227 803796 47618 23305 640948 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.644 -0.146 0.887 -0.299 -0.299 -0.299 -0.299 -0.292 0.685 -0.409 -0.236 0.67 -0.403 -0.403 -0.236 2.788 1.788 2.788 2.788 2.788 2.788 2.788 2.788 3.965 -2.51 0.481 3.933 -3.873 4.994 0.236 0.236 -1.499	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.681 0.511 0.681 0.521 0.681 0.521 0.682 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001	11 months after this date (Mar-20 to Jan		
sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 ydroxychloroquinesulfate-Model_2 ydroxychloroquinesulfate-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_5 .eflunomide-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_1 sulfasalazine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Azathioprine-Model_3 Methotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4 Wethotrexate-Model_4	(Step): Interact (After) TimePeriod Phase Interact	Estimate - 16503 - 46642 - 5626 - 4262 - 712710 - 29016 - 6734 - 573262 - 21531 - 6809 - 43938 - 15532 - 753 - 583 - 58732 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 2093 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 209 - 20 - 20 - 20 - 20 - 20 - 20 - 20 - 20	54217 1491083 88335 29227 803796 47618 22322 638927 37885 23305 639927 37885 37971 3188 87689 5195 5195 5195 5195 5195 5195 5195 51	-0.304 0.3 -0.644 -0.146 0.887 -0.299 -0.292 -0.887 -0.292 -0.292 -0.292 -0.236 -0.409 -0.236 -0.403 -0.403 -0.236 -2.51 -0.481 -2.51 -0.481 -3.873 -3.873 -3.873 -0.236	0.764 0.768 0.955 0.886 0.549 0.775 0.38 0.576 0.773 0.501 0.687 0.816 0.511 0.687 0.816 0.511 0.687 0.816 0.511 0.288 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.228 0.221 0.636 0.001 0.001 0.0001 0.0001 0.0001 0.0001 0.816			

ARIMA(0,0,0) Natural Logarithm, No	TimePeriod (Before); Phase	Parameter	Standard		
Transformation	(Step); Interact (After)	Estimate	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

time is β 1, for phase is β 2 and for interact is β 3 then the regression model is:

- 48
- 49
- 50
- 51
- 52
- 53
- 54 55
- 56 57
- 58
- 59
- 60

BMJ Open Page 2

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items 0221 0221-051936 0n 23	Location in manuscript where items are reported
Title and abstr	act			Dece	
	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 		RECORD 1.1: The type of glata used should be specified in the title or abstract. When possible, the name of the databases use should be included.	Title and abstract PG 1
		summary of what was done and what was found	r rei.	RECORD 1.2: If applicable the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Title and abstract PG 1
			6	RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	N/A
Introduction				April	
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		23, 2024 by guest.	In Introduction section (pg 4-)
Objectives	3	State specific objectives, including any prespecified hypotheses		Protected	End of Introduction section (pg 5)
Methods				by copyright	

3 of 32			BMJ Open	36/bmjop	
Study Design	4	Present key elements of study design early in the paper		pen-2021-05	PG 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		1936 on 23 Decemt	PG 5-6
				er 2022	•
Participants	6	 (a) Cohort study- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study-</i> 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 <i>Cross-sectional</i> <i>study-</i> 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 	or terie	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

Page 24 of 32	
---------------	--

			BMJ Open	36/bmjop	Pag
		<i>Case-control study-</i> For matched studies, give matching criteria and the number of controls per case		gen-2021-05193(
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete fist 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 - Quanti & 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	revie	http://bmjopen.bmj.com/ on April 23, 2024	PG 5-6, Pg 10, Original data are available from https://www.nhsk a.nhs.uk/prescrip on- data/prescribing- data/english- prescribing-data- epd
Bias	9	Describe any efforts to		by gues	N/A
Dias	7	address potential sources of bias		by guest. Protec	
Study size	10	Explain how the study size was arrived at		fied by copyright	PG 5

Page 2	5 of 32			BMJ Open										
1 2 3 4 5 6	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		3en-2021-051936 on	PG 5								
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	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 		April 23, 2	PG 5								
32 33 34 35 36 37 38 39 40	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 cru the study population.	e								
40 41 42 43 44 45 46 47			For peer review only - htt	tp://bmjopen.bmj.com/site/	the study population. Protected by copyright. /about/guidelines.xhtml									

BMJ	Open
-----	------

			BMJ Open	i6/bmjo	Pag
				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 databases. The methods of inkage quality evaluation should be provided.	None, N/A. Data Source.
Results		í Da		n load	·
Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, 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 	or terie	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , 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.	
				2024 by guest. Protected by copyright	
		For peer review only - htt	tp://bmjopen.bmj.com/site/	y copyright /about/guidelines.xhtml	

Page 2	7 of 32			BMJ Open		36/bmjop	
1 2 3 4 5 6 7 8 9 10 11 12 13	Descriptive data	14	 (a) Give characteristics of study participants (<i>e.g.</i>, 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) <i>Cohort study</i>- summarise follow-up time (<i>e.g.</i>, average and total amount) 			en-2021-051936 on 23 December 2022.	Results, Table 1 PG 6
14 15 16 17 18 19 20 21 22	Outcome data	15	<i>Cohort study-</i> Report numbers of outcome events or summary measures over time <i>Case-control study-</i> Report numbers in each exposure			Downloaded from http://bmj	Results, Table 1 PG 6
23 24 25				10	<u>b</u>	open.br	
26 27 28 29 30 31			category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		2001	nj.com/ on April 23,	
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47			For peer review only - htt	p://bmjopen.bmj.com/site/	'about/guidelines.xhtml	2024 by guest. Protected by copyright.	

			BMJ Open		Bi Di Page 28 d Di Page 28 d
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 			Page 28 of Page 28 of 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	r revie	h M	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					by guest. P
Key results	18	Summarise key results with reference to study objectives			PG 8

Page 2	9 of 32			BMJ Open	AJ Open							
1 2 3 4 5 6 7 8 9 10	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	at were answer the bar include fron bias, missing by over atudy	PG 9							
11 12 13 14 15	Interpretation	20	Give a cautious overall interpretation of results considering objectives,			2022. Down	PG 9-10					
16 17			DR			loaded t						
18 19 20 21 22 23			limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	r revi		from http://bmjop.						
24 25 26 27	Generalisability	21	Discuss the generalisability (external validity) of the study results	0	2	en.bmj.com/ o	PG 8-10					
28 29 30	Other Information	on		•	5	on April						
30 31 32 33 34 35 36 37	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		J.	23, 2024	PG 10					
38 39 40 41 42 43 44 45 46 47			For peer review only - htt	tp://bmjopen.bmj.com/site,	/about/guidelines.xhtml	by guest. Protected by copyright.						

			BMJ Open	36/bmjop	Page 30 of 3
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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
16 17				oa ded	

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

*Checklist is protected under Creative Commons Attribution (CC BY) license.

://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Page 31 of 32		BMJ Open	mjoper
¹ Supplementary Table 4	- Quantity & Cost		mjopen-2021-051936
2 3			05193
4 5			6 on 23
6 Supplemental Results (Total Quantity) 7 CHEMICAL_SUBSTANCE Jan-19 Feb-19			ل المحمد المحم المحمد المحمد المحم
8 Sulfasalazine 9.54 8.61 Hydroxychloroquine sulfate 4.89 4.37 9 Azathioprine 4.69 4.24		9.26 9.88 9.12 9.65 9.23 9.32 9.79 8.64 10.26 4.67 4.88 4.52 4.79 4.56 4.69 4.66 4.29 5.37 4.45 4.72 4.43 4.65 4.46 4.52 4.45 4.11 4.81	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Y Azamoprine 4.69 4.24 1 Qefluromide 4.19 3.81	4.12 4.05 4.32 3.98	4.45 4.72 4.43 4.65 4.46 4.52 4.45 4.11 4.81 4.11 4.39 4.05 4.31 4.13 4.26 4.27 3.90 4.54 0.54 0.59 0.53 0.57 0.55 0.56 0.56 0.51 0.60	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
1 Table 1 Total Quantity; Monthly Subtotal (in millions)			022.
12 1 Supplemental Results (Actual Cost) Medicine Jan-19 Feb-19	Mar 10 Apr 10 May 10 Jun 10 J	1419 Aug 10 Son 10 Oct 10 Nou 10 Doc 10 Jan 20 Eab 20 Mar 20	Apr-20 May-20 Jun-20 ≦Jul-20 Aug-20 Sep-20 Oct-20 Nov-20 Dec-20 Jan-21 Trend
4ulfasalazine 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	8 0.61 0.57 0.65 0.70 0.64 0.69 0.69 0.73 0.82 0.81
Hydroxychloroquine sulfate 0.30 0.27 1 Szathioprine 0.19 0.17 1 6/lethotrexate 3.27 3.12	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 3.75 4.01 3.85 4.15 4.02 4.21 4.29 3.96 4.70	8 0.61 0.57 0.60 0.70 0.64 0.69 0.73 0.82 0.81 2 0.77 0.55 0.40 0.51 0.46 0.50 0.54 0.53 0.55 0.57 6 0.59 0.47 0.46 0.27 0.24 0.26 0.24 0.23 0.24 0.25 0 4.47 4.26 4.67 4.33 4.65 4.68 4.56 4.94 4.63
Leflunomide 0.12 0.10 1 7Table 2 Actual Cost; Monthly Subtotal (in £millions) 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	2 0.10 0.10 0.11 0.10 0.10 0.10 0.09 0.10 0.09 ·····
18		0.20 0.23 0.21 0.22 0.21 0.22 0.32 0.20 0.56 3.75 4.01 3.85 4.15 4.02 4.21 4.29 3.96 4.70 0.11 0.13 0.12 0.12 0.12 0.12 0.12 0.11 0.12	n htt
19 20			p://t
21			mjo
22			pen.
23 24			b
25			Og
26			
27 28			Ap
29			
30 31			3, 20
32			24
33			
34 35			lest
36			Pro
37			tect
38 39			ed b
40			V CO
41			2 0.10 0.10 0.11 0.10 0.10 0.10 0.09 0.10 0.09 0.10
42 43	_		ght.
44	For pe	eer review only - http://bmjopen.bmj.com/site/about/gui	uidelines.xhtml
45			

Supplementary Table 5 - Region

Supplementary Table 5 - Region	
BMJ Open Supplementary Table 5 - Region	
O Total Quantity by region Jan 19 Feb-19 Mar 19 Apr 19 Mar 19 Jul-19 Jul-19 Aug 19 Sep 19 Otcl 19 Nov19 Dec 19 Jan 20 Feb-20 Mar 20 Jun-20 Jul-20 Aug 20 Sep 70 Out 20 Nov20 Dec -20 Jan -20 Feb-20 Mar 20 Jun -20 Aug 20 Sep 70 Out 20 Nov20 Dec -20 Jan -20 Feb-20 Mar 20 Aug -20 Jul-20 Aug 20 Sep 70 Out 20 Nov20 Dec -20 Jan -20 Feb-20 Mar 20 Aug -20 Jul-20 Aug 20 Sep 70 Out 20 Nov20 Dec -20 Jan -20 Feb 20 Mar 20 Aug -20 Aug -20 Jul-20 Aug 20 Sep 70 Out 20 Out 20 Sep 70 Out 20 Dec -20 Jan -20 Feb 20 Mar -20 Aug -20 Aug -20 Jul-20 Aug -20 Sep 70 Out 20 Out 20 Aug -20 Sep 70 Out 20 Aug -20 Sep 70 Out 20 Cold 20 Sep 70 Out 20 Sep 70 Out 20 Sep 70 Out 20 Sep 70 Out	vyvh vyvh vyvh vyvh
11 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 Trenc 12 Jorth 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
17 18 19 20 20 21 22 23 24 25 26 27 28 29 30 31 31 32 33 34 35 5	
26 27 28 29 30	
31 32 33 34 35	
36 37 37 38 39 by	
40 41 42 43 44 45	

Supplementary Table 6 - Methotrexate Quantity (in millions)

1 Supp	lementa	IY	lau	ne	0 -	IVIE	eun	00	EX	ale	u di	uai	itit	y (i			101	15)							
2																									
3																									
4																									
5																									
6																									
7 BNF DESCRIPTION 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	ec-20 Jan- 4.191
8 Methotrexate 50mg/2ml solution for injection vials Methotrexate 1g/10ml solution for injection vials Methotrexate 20mg/0.8ml inj pre-filled syringes	1001030U0BEARBW 1001030U0BEARBW 1001030U0BEAWCB	0.055 0.055 0.037	0.053 0.053 0.036	0.059 0.059 0.041	0.058 0.058 0.04	0.064 0.064 0.044	0.06 0.06 0.042	0.065 0.065 0.045	0.069 0.069 0.048	0.067 0.067 0.048	0.072 0.072 0.051	0.07 0.07 0.05	0.074 0.074 0.054	0.075 0.075 0.053	0.07 0.07 0.049	0.083 0.083 0.06	0.079 0.079 0.056	0.076 0.076 0.054	0.078 0.078 0.056	0.082 0.082 0.06	0.077 0.077 0.055	0.082 0.082 0.06	0.084 0.084 0.06	0.081 0.081 0.059	0.088 0.088 0.064
9 Methotrexate 22.5mg/0.9ml inj pre-filled syringes Methotrexate 25mg/1ml inj pre-filled syringes	1001030U0BEAWCB 1001030U0BEAXCC 1001030U0BEAXCC	0.037 0.036 0.036	0.036	0.041 0.04 0.04	0.04	0.044 0.043 0.043	0.042	0.045	0.048 0.046 0.046	0.048 0.044 0.044	0.051 0.049 0.049	0.05	0.054 0.048 0.048	0.053 0.048 0.048	0.049 0.046 0.046	0.06 0.054 0.054	0.056 0.052 0.052	0.054 0.049 0.049	0.056	0.06 0.054 0.054	0.055	0.06 0.054 0.054	0.06 0.056 0.056	0.059 0.053 0.053	0.064 0.058 0.058
Methotrexate 10mg/0.4ml inj pre-filled syringes Dethotrexate 7.5mg/0.3ml inj pre-filled syringes Methotrexate 12.5mg/0.5ml inj pre-filled syringes	100103000BEAXCC 1001030U0BEAZCE 1001030U0BEAZCE	0.036	0.035	0.018	0.04	0.043	0.019	0.044	0.048	0.044 0.021 0.021	0.049	0.045	0.048	0.048	0.048	0.025	0.052	0.023	0.023	0.034 0.024 0.024	0.051 0.022 0.022	0.034 0.024 0.024	0.056	0.023	0.025
Methotrexate 15mg/0.6ml inj pre-filled syringes Methotrexate 17.5mg/0.7ml inj pre-filled syringes Methotrexate 7.5mg/0.3ml inj pre-filled disposable	1001030U0AAACAC 1001030U0BEAQBV 1001030U0BEAQBV	0.035 0.01 0.01	0.031 0.009 0.009	0.032 0.01 0.01	0.03 0.011 0.011	0.032 0.011 0.011	0.029 0.011 0.011	0.029 0.011 0.011	0.029 0.013 0.013	0.027 0.012 0.012	0.028 0.012 0.012	0.026 0.013 0.013	0.026 0.013 0.013	0.025 0.013 0.013	0.022 0.012 0.012	0.025 0.015 0.015	0.023 0.014 0.014	0.021 0.013 0.013	0.022 0.014 0.014	0.021 0.014 0.014	0.019 0.013 0.013	0.019 0.015 0.015	0.019 0.015 0.015	0.017 0.014 0.014	0.02 0.016 0.016
Methotrexate 10mg/0.4ml inj pre-filled disposable Methotrexate 12.5mg/0.5ml inj pre-filled disposabl	1001030U0BEAYCD 1001030U0BEAYCD	0.008 0.008	0.009	0.009	0.009 0.009	0.01 0.01	0.009 0.009	0.01 0.01	0.01 0.01	0.01 0.01	0.011 0.011	0.011 0.011	0.011 0.011	0.011 0.011	0.011 0.011	0.013 0.013	0.012 0.012	0.011 0.011	0.012 0.012	0.013 0.013	0.012 0.012	0.013 0.013	0.013 0.013	0.013 0.013	0.014 0.014
Bethotrexate 15mg/0.6ml inj pre-filled disposable Methotrexate 17.5mg/0.7ml inj pre-filled disposabl Methotrexate 20mg/0.8ml inj pre-filled disposable	1001030U0BDAAAB 1001030U0BEASBX 1001030U0BEASBX	0.013 0.005 0.005	0.011 0.005 0.005	0.012 0.006 0.006	0.012 0.006 0.006	0.013 0.007 0.007	0.011 0.006 0.006	0.012 0.006 0.006	0.013 0.007 0.007	0.012 0.006 0.006	0.012 0.007 0.007	0.011 0.007 0.007	0.012 0.007 0.007	0.011 0.008 0.008	0.011 0.007 0.007	0.013 0.009 0.009	0.011 0.009 0.009	0.011 0.008 0.008	0.011 0.008 0.008	0.012 0.009 0.009	0.01 0.008 0.008	0.01 0.009 0.009	0.011 0.009 0.009	0.01 0.009 0.009	0.011 0.009 0.009
Auethotrexate 22.5mg/0.9ml inj pre-filled disposabl Methotrexate 25mg/1ml inj pre-filled disposable de	1001030U0BEATBY 1001030U0BEATBY	0.006 0.006	0.005	0.006	0.006 0.006	0.007	0.006	0.007	0.007	0.007 0.007	0.008	0.007	0.008	0.007	0.007	0.008	0.008	0.007 0.007	0.008	0.008	0.008 0.008	0.008 0.008	0.008 0.008	0.008	0.009
Jatal 20mg/0.8ml solution for injection pre-fille Jatal 22.5mg/0.9ml inj pre-filled syringes Zlatal 25mg/1ml solution for injection pre-filled	1001030U0AABWBW 1001030U0AACCCC 1001030U0AACBCB	0.01 0.006 0.006	0.009 0.006 0.005	0.009 0.006 0.006	0.009 0.006 0.006	0.01 0.006 0.006	0.009 0.006 0.005	0.009 0.006 0.005	0.009 0.006 0.005	0.008 0.005 0.005	0.009 0.006 0.005	0.008 0.005 0.005	0.008 0.006 0.005	0.008 0.005 0.005	0.007 0.005 0.004	0.008 0.006 0.005	0.008 0.005 0.005	0.007 0.005 0.005	0.007 0.005 0.004	0.007 0.005 0.004	0.006 0.004 0.004	0.007 0.005 0.004	0.006 0.004 0.004	0.006 0.004 0.004	0.006 0.004 0.004
Jatal 10mg/0.4ml solution for injection pre-fille Zlatal 7.5mg/0.3ml inj pre-filled syringes	1001030U0AACFCF 0801030P0BFAFFS	0.003 0.001	0.003 0.001	0.003	0.002 0.001	0.002 0.001	0.002	0.002	0.002 0.001	0.003 0.001	0.002 0.002	0.003 0.001	0.002	0.003	0.003	0.003	0.002	0.003	0.003	0.003	0.002 0.002	0.002 0.002	0.003	0.003	0.003
Zatal 12.5mg/0.5ml inj pre-filled syringes Zlatal 15mg/0.6ml solution for injection pre-fille Zlatal 17.5mg/0.7ml inj pre-filled syringes	0801030P0BFADFQ 1001030U0AACECE 0801030P0BFAHFU	0.001 0.003	0.001 0.003 0.001	0.001 0.002 0.001	0.001 0.003 0.001	0.001 0.003 0.001	0.001 0.002 0.001	0.002 0.002 0.001																	
Sordimet 7.5mg/0.3ml solution for injection pre-fi	1001030U0AABVBV 1001030U0AABHBH	0.002	0.002 0.	0.001 0.	0.002 0.	0.001 0.	0.002	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									
Nordimet 10mg/0.4ml solution for injection pre-fil Ordimet 12.5mg/0.5ml solution for injection pre-fil Nordimet 15mg/0.5ml solution for injection pre-fil Nordimet 17.5mg/0.7ml solution for injection pre-fil	1001030U0AACDCD 1001030U0AABXBX 1001030U0AABYBY	0.001 0.001 0.001																							
Optimet 20mg/0.8ml solution for injection pre-fil Nordimet 22.5mg/0.9ml solution for injection pre-f	1001030U0AABGBG 0801030P0BFABFN	0. 0.	0. 0.001	0. 0.001	0. 0.	0. 0.001	0. 0.001	0. 0.001	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										
2 Nordimet 25mg/1ml solution for injection pre-fille Methotrexate 2.5mg tablets Methotrexate 10mg tablets	0801030P0AAFSFS 1001030U0AAAEAE 1001030U0BGAFBW	0.001 0. 0	0.001 0. 0	0.001 0. 0	0.001 0. 0	0.001 0. 0	0.001 0. 0	0.001 0. 0.001	0.001 0. 0	0.001 0. 0	0.001 0.001 0.001	0.001 0. 0.001	0.001 0. 0.001	0.001 0. 0	0.001 0. 0	0.001 0.001 0.001	0.001 0. 0	0.001 0.	0.001	0.001 0. 0.001	0.001 0. 0.001	0.001 0. 0.001	0.001 0. 0.001	0.001 0. 0.001	0.001 0. 0.001
22 Nethotrexate 10mg tablets Methotrexate 2.5mg/5ml oral liquid Methotrexate 5mg/5ml oral liquid	1001030U0BEAVCA 1001030U0BEAVCA	0. 0.	0. 0.	0. 0.	0. 0.	0. 0.	0. 0.	0.001	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	0.001 0.001
2 3lethotrexate 10mg/5ml oral liquid Methotrexate 7.5mg/5ml oral liquid Methotrexate 12.5mg/5ml oral liquid	0801030P0AAFUFU 0801030P0AAFQFQ 1001030U0AABIBI	0. 0.001	0. 0.001	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	0.001
Attention of the second sec	1001030U0AABFBF 0801030P0BFAEFR	0. 0.																							
2 Stethotrexate 15mg/1.5ml inj pre-filled syringes Stethotrexate 7.5mg/0.15ml inj pre-filled syringes Methotrexate 10mg/0.2ml inj pre-filled syringes	1001030U0BGADCC 1001030U0BGAHCB 0801030P0AAFEFE	0. 0.																							
A gethotrexate 15mg/0.3ml inj pre-filled syringes Methotrexate 20mg/0.4ml inj pre-filled syringes	0801030P0BFACFP 0801030P0BFACFP 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. 0.														
2 Thethotrexate 25mg/0.5ml inj pre-filled syringes Methotrexate 30mg/0.6ml inj pre-filled syringes	0801030P0AAFGFG 0801030P0AAFNFN 0801030P0BFAAFM	0. 0.	0. 0.	0. 0.	0. 0.	0.	0. 0.	0.	0. 0.																
Methotrexate 12.5mg/0.25ml inj pre-filled syringes dethotrexate 17.5mg/0.35ml inj pre-filled syringes Methotrexate 22.5mg/0.45ml inj pre-filled syringes	0801030P0BPAAPM 0801030P0AAFKFK 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. 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. 0.	0. 0. 0.	0. 0. 0.	0. 0. 0.
Methotrexate 22.5mg/0.45ml inj pre-filled syringes 2 Grethotrexate 17.5mg/0.35ml inj pre-filled disposab Wiethotrexate 20mg/0.4ml inj pre-filled disposable	1001030U0BDABAC 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.	0. 0.	0. 0.	0.	0. 0.	0.	0. 0.	0. 0.	0.	0. 0.
Methotrexate 22.5mg/0.45ml inj pre-filled disposab Dethotrexate 7.5mg/0.15ml inj pre-filled disposabl Methotrexate 27.5mg/0.55ml inj pre-filled disposab	1001030U0BGABCE 0801030P0AAFRFR 0801030P0BEAAFE	0. 0. 0.																							
3 Methotrexate 30mg/0.6ml inj pre-filled disposable Methotrexate 25mg/0.5ml inj pre-filled disposable	0801030P0AAFPFP 1001030U0AABEBE 0801030P0BEAGFK	0. 0.	0.	0. 0.																					
32 Methotrexate 15mg/0.3ml inj pre-filled disposable Methotrexate 12.5mg/0.25ml inj pre-filled disposab Methotrexate 10mg/0.2ml inj pre-filled disposable	1001030P0BEAGFK 1001030U0BEAUBZ 1001030U0BEAUBZ	0. 0. 0.																							
3 3 iethotrexate 2mg/ml oral solution sugar free Maxtrex 2.5mg tablets Maxtrex 10mg tablets	0801030P0AAFHFH 1001030U0BGAEBV 1001030U0AABMBM	0. 0.																							
34 etoject 20mg/2ml solution for injection pre-fille Metoject 10mg/1ml solution for injection pre-fille	080103000AABMBM 0801030P0AAFMFM 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. 0. 0.	0. 0. 0.	0. 0.	0. 0. 0.	0. 0. 0.	0. 0.	0. 0.	0. 0.	0. 0. 0.						
3 Stetoject 15mg/1.5ml inj pre-filled syringes Metoject 25mg/2.5ml inj pre-filled syringes Metoject 7.5mg/0.15ml inj pre-filled syringes	0801030P0BEACFG 0801030P0AAFTFT 1001030U0AAAHAH	0. 0.	0. 0.	0. 0.	0. 0.	0. 0. 0.001	0. 0.																		
3 (petoject 10mg/0.2ml inj pre-filled syringes	1001030U0BGAPBH 0801030P0AAFLFL	0. 0.	0. 0.	0. 0.	0. 0.	0.	0. 0.																		
3 Thetoject 20mg/0.4ml inj pre-filled syringes Metoject 25mg/0.5ml inj pre-filled syringes	1001030U0BGAGBX 0801030P0AAFFFF 1001030U0BGAABY	0. 0.																							
Hetoject 12.5mg/0.25ml inj pre-filled syringes Gietoject 17.5mg/0.35ml inj pre-filled syringes Metoject 22.5mg/0.45ml inj pre-filled syringes	1001030U0BGAABY 0801030P0AAFIFI 1001030U0BGARBI	0. 0. 0.	0. 0. 0.	0. 0. 0.	U. 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.	0. 0. 0.	0. 0. 0.	0. 0.	0. 0. 0.								
3 Detoject PEN 17.5mg/0.35ml inj pre-filled pens Netoject PEN 17.5mg/0.35ml inj pre-filled pen	1001030U0BGAMBG 0801030P0AAFJFJ 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. 0.							
Metoject PEN 20mg/0.4ml inj pre-filled pens detoject PEN 20mg/0.4ml inj pre-filled pen Metoject PEN 22.5mg/0.45ml inj pre-filled pens	1001030U0AACACA 0801030P0BEADFH 0801030P0BEAEFI	0. 0. 0.																							
Metoject PEN 22.5mg/0.45ml inj pre-filled pen Metoject PEN 7.5mg/0.15ml inj pre-filled pen	1001030U0AABZBZ 0801030P0BEAHFL	0. 0.	0.	0. 0.																					
Metoject PEN 7.5mg/0.15ml inj pre-filled pens Dietoject PEN 27.5mg/0.55ml inj pre-filled pens Metoject PEN 27.5mg/0.55ml inj pre-filled pen	1001030U0BEACBB 1001030U0BGAQBM 1001030U0BGAUBK	0. 0. 0.																							
Netoject PEN 30mg/0.6ml inj pre-filled pens Netoject PEN 30mg/0.6ml inj pre-filled pen	0801030P0BEABFF 1001030U0BEAMBL	0. 0.	0.	0. 0.	0.	0. 0.																			
etoject PEN 25mg/0.5ml inj pre-filled pens etoject PEN 25mg/0.5ml inj pre-filled pen etoject PEN 15mg/0.3ml inj pre-filled pen	0801030P0BEAFFJ 1001030U0BEAIBH 1001030U0BEAGBF	0. 0.	0.	0. 0.	0. 0.	0. 0.	0. 0.	0. 0.	0. 0.	0. 0. 0															
oject PEN 15mg/0.3ml inj pre-filled pens oject PEN 12.5mg/0.25ml inj pre-filled pens	1001030U0BEAHBG 1001030U0BEAJBI	0. 0.																							
ject PEN 12.5mg/0.25ml inj pre-filled pen ject PEN 10mg/0.2ml inj pre-filled pens ject PEN 10mg/0.2ml inj pre-filled pen	1001030U0BEALBK 1001030U0BGAKBE 1001030U0BGANBL	0. 0.																							
thofill 7.5mg/0.15ml inj pre-filled injector thofill10mg/0.2ml inj pre-filled injector	1001030U0BEADBC 0801030P0AAAIAI	0. 0.																							
lethofill 12.5mg/0.25ml inj pre-filled injector lethofill 15mg/0.3ml inj pre-filled injector	0801030P0AAANAN 0801030P0AACKCK 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. 0.	0. 0.							
Methofill 17.5mg/0.35ml inj pre-filled injector Nethofill 20mg/0.4ml inj pre-filled injector Methofill 22.5mg/0.45ml inj pre-filled injector	1001030U0AAAIAI 1001030U0AAAKAK	0. 0. 0.	0. 0. 0.	0. 0.	U. 0. 0.	0. 0. 0.	0. 0.	0. 0. 0.																	
Methofill 25mg/0.5ml inj pre-filled injector	1001030U0AAARAR 1001030U0AABABA 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. 0.							
Methofill 7.5mg/0.15ml inj pre-filled syringes Methofill 10mg/0.2ml inj pre-filled syringes Methofill 15mg/0.3ml inj pre-filled syringes	1001030U0AABCBC 1001030U0AABJBJ 1001030U0BEABBA	0. 0. 0.																							
5 Methofill 17.5mg/0.35ml inj pre-filled syringes Methofill 20mg/0.4ml inj pre-filled syringes	1001030U0BEAEBD 1001030U0BEAFBE	0. 0.																							
Methofill 22.5mg/0.45ml inj pre-filled syringes 53hethofill 25mg/0.5ml inj pre-filled syringes hethofill 12.5mg/0.25ml inj pre-filled syringes	1001030U0BEANBM 1001030U0BGAIBZ 1001030U0BGALBF	0. 0. 0.																							
54		v.	0.	U.	U.	υ.	υ.	U.	v.	U.	v.	U.	U.	U.	0.	U.	υ.	υ.	υ.	U.	U.	U.	U.	σ.	<i>v.</i>
55	Sum Total (Methotrexate) Sum of top ten rows (10010:	4.368	3.977	4.306	4.232	4.529	4.177	4.321	4.615	4.267	4.546 4.415	4.357	4.502	4.508	4.125	4.81	4.516	4.318	4.47 4.332	4.661	4.229	4.557	4.6 4.459	4.438	4.829
56	% 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%
57																									
58																									
-																									

59 60 4.829 4.439 4.68 4.299 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

SCHOLARONE[™] Manuscripts



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 <u>licence</u>.

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 <u>Creative Commons</u> 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.

relievont

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:

- <u>corresponding author</u> Mrs. Ravina Barrett (<u>https://orcid.org/0000-0003-0004-</u> 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 <u>rob-barrett@outlook.com</u>; <u>https://orcid.org/0000-0003-3402-3377</u> 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, <u>X.Lin@soton.ac.uk</u>
- 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, <u>d.j.culliford@soton.ac.uk</u>
- 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 (<u>https://orcid.org/</u>) <u>S.Fraser@soton.ac.uk</u>.
- 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, 11months 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

tor beer terien only

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

58 59

60

(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 pandemicguidelines.[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 commaseparated 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

1 2

3 4

5

6

7 8

9

10

11

12

13

14

15

16 17

18

19

20

21

22

23

24

25 26

27

28 29

30

31

36

37

38

39 40

41

42

43

44

45 46

47

48

49

50

51

52

53

54 55

56

57

58

59

60

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 p	bandemic			After Pa	ndemic's	Onset		Total Qu	antity	Actual C	Cost (£)
Medicine	Mean	SD	UCI	LCI	Mean	SD	UCI	LCI	Mean	SD	Mean	SD
Sulfasalazine Hydroxychloroquine	9.303	0.384	9.504	9.102	9.267	0.468	9.544	8.991	9.28	0.422	0.628	0.039
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:

- 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.
- 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.
- 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 antirheumatics 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)	Parameter Estimate	Standard Error	T-statistic	P-value	Lower Cl	Upper Cl
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.

to perterien on

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] <u>https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd</u> 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/nhsservices/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/healthand wellbeing/articles/nhs70marking70yearsofthenationalhealthservice/2018-06-26 (accessed 12 Oct 2022).
- 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-usesof-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.

2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
ר ∠ בר	
22	
23	
4 5 6 7 8 9 10 11 23 4 5 6 7 8 9 10 11 23 24 25 26 27 28 29 30 12 33 34 35 36 37 89	
25	
26	
27	
28	
29	
30	
31	
27	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
42 43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
52 53	
54	
55	
56	
57	
58	
59	
60	

- 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-lessonslearned-to-date-report-government-response/the-governments-response-to-the-health-andsocial-care-committee-and-science-and-technology-committee-joint-report-coronaviruslessons-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_documentsupply_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.

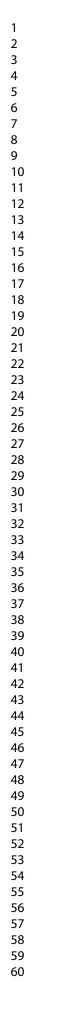
Figure 2 ARIMA (0,0,0)(0,0,0) Prescription volumes for individual medicines (a)Sulfasalazine; (b)Hydroxychloroquine sulfate; (c)Azathioprine; (d)Methotrexate; (e)Leflunomide.

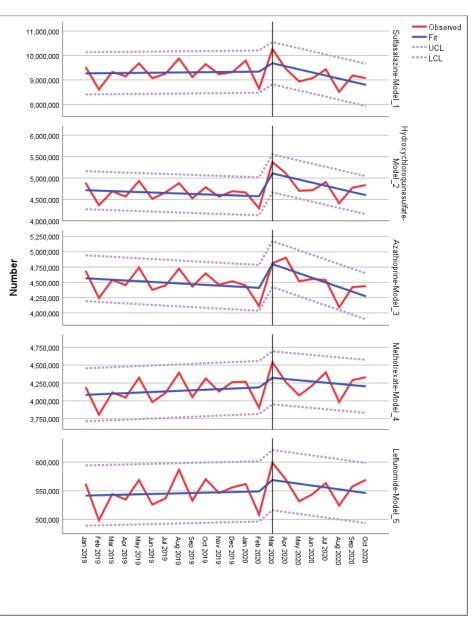
Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

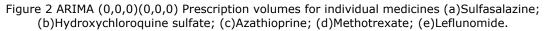
, or inda .er March and Iowe.

1		
2		
3		
4		
5		
6	12,470,000	Sulfasalazine
7	12,470,000	Hydroxychloroquinesulfate
8	10,470,000	
9	8,470,000	
10	-11	
11	6,470,000	
12 13		
14	4,470,000	
15		1
16	2,470,000	
17	2,470,000	
18		
19		
20		÷ ÷
21	470,000	
22		0 1
23	I	Phase (0 is pre-pandemic Jan19-Feb20, 1 is post-lockdown Mar20-Jan19)
24		
25		
26	Figure 1 Box p	lot representing mean values before the pandemic and after its onset. Quantities are
27		presented in absolute numbers.
28		300x176mm (72 x 72 DPI)
29		
30		
31 32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
49 50		
50 51		
52		
53		
54		
55		
56		
57		
58		
59		
	E	en ne en neu deux en la collecter d'Anné en en la set en ne (eitre (els eu triminal elles en ult trad
60	F	or peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open







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)

BMJ Open: first published as 10.1136/bmjopen-2021-051936 on 23 December 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Page 24 of 38

DATASE	ACTIVATE DataSet3.
PREDICT	THRU END.
* Time Se	ies Modeler.
TSMODE	
/MODEI	SUMMARY PRINT=[MODELFIT]
	STATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
	DETAILS PRINT=[PARAMETERS]
	PLOT OBSERVED FIT FORECASTCI FITCI
	TFILTER DISPLAY=ALLMODELS
	PREDICTED(Predicted) LCL(LCL) UCL(UCL)
	RY CILEVEL=95 MAXACFLAGS=24
	G USERMISSING=EXCLUDE
	DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Le
e	
	NDENT=TimePeriod Phase Interact
	AR=[1] DIFF=0 MA=[0]
	SFORM=NONE CONSTANT=YES
	UTLIER DETECT=OFF.
740100	
	THRU END.
* Time Se	ies Modeler.
TSMODE	
/MODEI	SUMMARY PRINT=[MODELFIT]
/MODEI	STATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
/MODEI	DETAILS PRINT=[PARAMETERS]
/SERIE	PLOT OBSERVED FIT FORECASTCI FITCI
/OUTPL	TFILTER DISPLAY=ALLMODELS
/SAVE	REDICTED(Predicted) LCL(LCL) UCL(UCL)
/AUXILI	RY CILEVEL=95 MAXACFLAGS=24
/MISSIN	G USERMISSING=EXCLUDE
/MODEI	DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Le
е	
	NDENT=TimePeriod Phase Interact
	X='Model'
	AR=[0] DIFF=1 MA=[0]
	SFORM=NONE CONSTANT=YES
/AUTOC	UTLIER DETECT=OFF.
PREDICT	THRU END.
* Time Se	ies Modeler.
TSMODE	
/MODEI	SUMMARY PRINT=[MODELFIT]
	STATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
	DETAILS PRINT=[PARAMETERS]
	PLOT OBSERVED FIT FORECASTCI FITCI
	TFILTER DISPLAY=ALLMODELS
	RY CILEVEL=95 MAXACFLAGS=24

BMJ Open

1	
2	
3	
4	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
5	
6	INDEPENDENT=TimePeriod Phase Interact
7	PREFIX='Model'
8	/ARIMA AR=[0] DIFF=0 MA=[1]
9	TRANSFORM=NONE CONSTANT=YES
10 11	/AUTOOUTLIER DETECT=OFF.
12	
12	PREDICT THRU END.
14	* Time Series Modeler.
15	TSMODEL
16	/MODELSUMMARY PRINT=[MODELFIT]
17	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
18	/MODELDETAILS PRINT=[PARAMETERS]
19	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
20	/OUTPUTFILTER DISPLAY=ALLMODELS
21	AUXILIARY CILEVEL=95 MAXACFLAGS=24
22	/MISSING USERMISSING=EXCLUDE
23 24	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
25	е
26	INDEPENDENT=TimePeriod Phase Interact
27	PREFIX='Model'
28	/ARIMA AR=[0] DIFF=0 MA=[0]
29	TRANSFORM=LN CONSTANT=YES
30	/AUTOOUTLIER DETECT=OFF.
31	
32	
33 34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44 45	
45 46	
47	
48	
49	
50	
51	
52	
53	
54	
55 56	
50 57	
58	
59	
60	

BMJ Open

1 2	ARIMA Model Parameters	ARIMA (March20+ is a '1')	Total Quanti 14 months (J		0) before th	ie COVID-19) first lockdo	own in Englan	nd (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21)
3		TimePeriod (Before); Phase	Parameter	Standard					
4	ARIMA(0,0,0), No Transformation	(Step); Interact (After)	Estimate	Error	T-stat			.CI	
5	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	5435 659017		0.188 0.752	0.852	65021 2466774	-54151 -1148740	Confidence intervals were calculated as (24df): Cl=parameter+/-tinv(0.05, df)*SE
6	Sulfasalazine-Model_1	Interact	-38151			0.459	66220	-142522	
7	Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955			0.453	18632	-40543	
8	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	814729 -24392			0.075	1712394 27434	-82935 -76219	
	Azathioprine-Model_3	TimePeriod	-12052			0.337	13278	-37382	
9	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	786705 -31340		2.113	0.047 0.16	<u>1555182</u> 13028	<u>18229</u> - 75708	
10	Methotrevate-Model 4	TimePeriod	7966	11836		0.508	32395	-16462	
11	Methotrexate-Model_4 Methotrexate-Model_4	Phase Interact	249614 -10634			0.495 0.613	990758 32156	-491531 -53424	
12	Leflunomide-Model_5	TimePeriod	561	1662	0.338	0.739	3992	-2870	
13	Leflunomide-Model_5 Leflunomide-Model_5	Phase Interact	30388 -1188			0.553 0.687	134482 4822	-73706 -7198	
14		interdet	1100		0.100	0.007	1022	,130	
		TimePeriod (Before); Phase	Parameter						
15	ARIMA(1,0,0), AR	(Step); Interact (After)	Estimate	Standard Erro				.CI	
	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	19759 417103		0.977 0.678	0.34 0.505	61517 1686169	-21999 -851964	the coefficient for 'time' gives us the slope of the regression line pre-intervention the coefficient for 'phase' gives us the change in intercept
17	Sulfacelezing Model 1	Interact	-37930			0.291	34250	-110110	the coefficient for 'interact' gives us the change in slope post intervention
18	Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	-5175 700712			0.644 0.05	17613 1393748	-27962 7675	If the coefficient for time is β 1, for phase is β 2 and for interact is β 3 then the regression model is:
	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Interact	-23233			0.05	1393748	-62654	in the coefficient for time is p2, for phase is p2 and for interact is p3 then the regression model is:
	Azathioprine-Model_3	TimePeriod	-9123			0.394	12476	-30722	Therefore, pre intervention becomes:
	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	738472 -31213		2.326 -1.73	<u>0.031</u> 0.099	<u>1393704</u> 6021	83240 -68447	Outcome = constant + β1time
21	Methotrevate-Model 4	TimePeriod	14064			0.064	28852	-724	
	Methotrexate-Model_4 Methotrexate-Model_4	Phase Interact	86932 -7128			0.695 0.572	538582 18463	-364718 -32718	Outcome= constant + β 1time + β 2 + β 3interact = (constant + β 2) + (β 1 + β 3) time (as time and interact are the same post intervention)
	Leflunomide-Model_5	TimePeriod	1432	1106	1.295	0.21	3714	-850	
24	Leflunomide-Model_5 Leflunomide-Model_5	Phase Interact	-882			0.746 0.649	80661 3063	-58520 -4827	
25									
26		TimePeriod (Before); Phase	Parameter						
	ARIMA(0,1,0), Difference	(Step); Interact (After)	Estimate	Standard Erro				.CI	
27	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	-16503 446642		-0.304	0.764	95395 3524086	-128402 -2630801	
28	Sulfasalazine-Model_1 Sulfasalazine-Model_1	Interact	-5626	88335	-0.064	0.95	176688	-187940	
29	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	-4262 712710			0.886	56059 2371664	-64583 -946244	
30	Hydroxychloroquinesulfate-Model_2	Interact	-29016			0.549	69263	-127296	
31	Azathioprine-Model_3 Azathioprine-Model_3	TimePeriod Phase	-6734 573262		-0.29 0.897	0.775 0.38	41214 1891942	-54683 -745419	
		Interact	-21531		-0.569	0.576	56590	-99652	
32	Azathioprine-Model_3 Methotrexate-Model_4 Methotrexate-Model_4	TimePeriod	-6809			0.773	41292	-54909	
33	Methotrexate-Model_4	Phase Interact	439338 -15532			0.501 0.687	1762190 62837	-883514 -93900	
	Leflunomide-Model_5	TimePeriod	-753			0.816	5828	-7333	
	Leflunomide-Model_5 Leflunomide-Model_5	Phase Interact	58732 -2093		0.67 -0.403	0.511 0.691	239712 8629	-122249 -12814	
36									
37		TimePeriod (Before); Phase	Parameter						
	ARIMA(0,0,1), MA Sulfasalazine-Model_1	(Step); Interact (After) TimePeriod	Estimate 27834	Standard Erro	T-stat 2.788	P-value 0.011	UCI L 48437	.CI 7231	
20	Sulfasalazine-Model_1	Phase	459301			0.288	1328214	-409613	
39	Sulfasalazine-Model_1 Sulfasalazine-Model_1	Interact TimePoriod	-50867			0.028	<u>-6402</u>	<u>-95332</u>	
40	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	1157 637368			0.826 0.006	11859 <u>1066559</u>	-9545 <u>208178</u>	
41	Hydroxychloroquinesulfate-Model_2	Interact TimePoriod	-26929	10730	-2.51	<u>0.021</u>	<u>-4783</u>	<u>-49075</u>	
42	Azathioprine-Model_3 Azathioprine-Model_3	TimePeriod Phase	-2278 660176			0.636 0.001	7505 1006868	-12062 313483	
43	Azathioprine-Model_3 Methotrexate-Model_4	Interact	-34495	8907	-3.873	<u>0.001</u>	<u>-16113</u>	<u>-52878</u>	
ΔΛ	Methotrexate-Model_4 Methotrexate-Model_4	TimePeriod Phase	18549 27587			0.00007 0.816	<u>26214</u> 268434	<u>10884</u> - 213260	
	Methotrexate-Model_4	Interact	-8773	5851	-1.499	0.149	3304	-20850	
_	Leflunomide-Model_5 Leflunomide-Model_5	TimePeriod Phase	2037 -1004			<u>0.001</u> 0.957	<u>3157</u> 37104	<u>917</u> -39112	
46	Leflunomide-Model_5	Interact	-931			0.356	1102	-2965	
47									
48	ARIMA(0,0,0) Natural Logarithm, No		Parameter		T - 4 - 5	D. und		C	
49	Transformation Sulfasalazine-Model_1	(Step); Interact (After) Sulfasalazine	Estimate 16.041	Error 0.026				CI 15.987339	
	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod	0.001	0.003	0.179	0.86	0.007	-0.005	
50 E 1	Sulfasalazine-Model_1 Sulfasalazine-Model_1	Phase Interact	0.067			0.488	0.261 0.006	-0.127 -0.014	
_	Hydroxychloroquinesulfate-Model_2	Hydroxychloroquinesulfate	15.368	0.026	597.458	0	15.422	15.314	
	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	-0.002 0.163			0.445 0.09	0.004	-0.008 -0.027	
53	Hydroxychloroquinesulfate-Model_2	Interact	-0.005	0.005	-0.887	0.385	0.005	-0.015	
54	Azathioprine-Model_3 Azathioprine-Model_3	Azathioprine TimePeriod	15.336 -0.003			0 0.335	15.383 0.003	15.289 -0.009	
55	Azathioprine-Model_3 Azathioprine-Model_3	Phase	-0.003			0.335	0.003	-0.009	
	Azathioprine-Model_3	Interact Mothetrevate	-0.007			0.175	0.003	-0.017	
	Methotrexate-Model_4 Methotrexate-Model_4	Methotrexate TimePeriod	15.22 0.002			0 0.499	15.270 0.008	15.170 -0.004	
57	Methotrexate-Model_4 Methotrexate-Model_4	Phase	0.059	0.086	0.687	0.5	0.236	-0.118	
58	Methotrexate-Model_4 Leflunomide-Model_5	Interact Leflunomide	-0.003 13.2			0.614 0	0.007 13.254	-0.013 13.146	
59	Leflunomide-Model_5	TimePeriod	0.001	0.003	0.348	0.731	0.007	-0.005	
60	Leflunomide-Model_5 Leflunomide-Model_5	Phase Interact	0.054			0.565	0.244 0.008	-0.136 -0.012	
			0.002	0.005	0.350	0.050	0.000	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 (23^d Mar-20) until 11 months after this date (Mar-20 to Jan-21).

Page 27 of 38

1								
1 2	ARIMA Model Parameters	ARIMA (March20+	is a '0')					
2	ARIMA(0,0,0), No Transformation		Estimate	Standard Error	r i	P-value	UCI	LCI
	Sulfasalazine-Model_1	TimePeriod	0.003	0.003	1.091		0.009192	-0.00319
4	Sulfasalazine-Model_1	Phase	-0.047		-0.449		0.169709	-0.26371
5	Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model 2	Interact TimePeriod	-0.001 0.002	0.006 0.003	-0.091 0.565		0.011383 0.008192	-0.01338 -0.00419
6	Hydroxychloroquinesulfate-Model 2	Phase	0.08	0.122	0.655		0.331796	-0.1718
7	Hydroxychloroquinesulfate-Model_2	Interact	-0.004	0.006	-0.618	0.543	0.008383	-0.01638
8	Azathioprine-Model_3	TimePeriod	0		-0.167		0.006192	-0.00619
9	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	0.152 -0.008	0.105 0.006	1.451 -1.362		0.368709 0.004383	-0.06471 -0.02038
	Methotrexate-Model 4	TimePeriod	0.004	0.003	1.552		0.010192	
10	Methotrexate-Model_4	Phase	-0.017	0.1	-0.171	0.866	0.18939	-0.22339
11	Methotrexate-Model_4	Interact	-0.001		-0.113		0.009319	-0.01132
12	Leflunomide-Model_5 Leflunomide-Model 5	TimePeriod Phase	0.003 -0.03	0.003 0.106	1.193 -0.285		0.009192 0.188773	-0.00319 -0.24877
13	Leflunomide-Model_5	Interact	0.00006631	0.006	0.012	0.991	0.01245	-0.01232
14								
15	ARIMA(1,0,0), AR		Estimate	Standard Error		P-value		LCI
16	Sulfasalazine-Model 1	TimePeriod	0.003	0.002	1.716		0.007128	
	Sulfasalazine-Model_1	Phase	-0.033	0.071	-0.459	0.651	0.113537	-0.17954
17	Sulfasalazine-Model_1	Interact	-0.001		-0.328		0.007256	-0.00926
18	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	0.002 0.092	0.002 0.094	0.722 0.983		0.006128 0.286006	-0.00213 -0.10201
19	Hydroxychloroquinesulfate-Model 2	Interact	-0.004		-0.907		0.006319	-0.01432
20	Azathioprine-Model_3	TimePeriod	0		-0.143		0.004128	
21	Azathioprine-Model_3	Phase	0.153	0.088	1.744		0.334623	-0.02862
22	Azathioprine-Model_3 Methotrexate-Model 4	Interact TimePeriod	-0.008 0.004	0.005	-1.677 2.719		0.002319 0.006064	-0.01832
	Methotrexate-Model_4	Phase	-0.019	0.059	-0.323	0.75	0.10277	-0.14077
23	Methotrexate-Model_4	Interact	0	0.003	-0.117	0.908	0.006192	-0.00619
24	Leflunomide-Model_5	TimePeriod	0.004	0.002	2.073 -0.498		0.008128	
25	Leflunomide-Model_5 Leflunomide-Model 5	Phase Interact	-0.034 0		0.056		0.106345 0.008256	-0.17435 -0.00826
26								
27								
28	ARIMA(0,1,0), Difference Sulfasalazine-Model 1	TimePeriod	Estimate 0.004	Standard Error 0.005	t 0.721	P-value	0.014319	LCI -0.00632
29	Sulfasalazine-Model_1	Phase	-0.142		-0.786		0.231566	
	Sulfasalazine-Model_1	Interact	0.004	0.01	0.417	0.681	0.024639	-0.01664
30	Hydroxychloroquinesulfate-Model_2	TimePeriod	0.006	0.005	1.089		0.016319	-0.00432
31	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model 2	Phase Interact	-0.073 -0.001	0.193 0.01	-0.38 -0.084		0.325332 0.019639	-0.47133 -0.02164
32	Azathioprine-Model_3	TimePeriod	0.003	0.005	0.741		0.013319	-0.00732
33	Azathioprine-Model_3	Phase	-0.018	0.168	-0.109		0.328735	-0.36473
34	Azathioprine-Model_3	Interact TimePeriod	-0.002	0.009 0.005	-0.196 0.638		0.016575	-0.02058
35	Methotrexate-Model_4 Methotrexate-Model_4	Phase	0.003 -0.041	0.003	-0.228		0.013319 0.326374	-0.00732 -0.40837
	Methotrexate-Model_4	Interact	-0.001	0.01	-0.06		0.019639	-0.02164
36	Leflunomide-Model_5	TimePeriod	0.004	0.005	0.731		0.014319	-0.00632
37	Leflunomide-Model_5 Leflunomide-Model_5	Phase Interact	-0.054 0		-0.291 -0.025		0.325757 0.020639	-0.43376 -0.02064
38	lenanomiae model_o	interact	0	0.01	0.025	0.501	0.020000	0.02001
39								
40	ARIMA(0,0,1), MA, Natural Log Sulfasalazine-Model 1	TimePeriod	Estimate 0.003	Standard Error 0.001	t 3.399	P-value	0.005064	LCI
41	Sulfasalazine-Model_1	Phase	0.003	0.054	0.015		0.112451	
42	Sulfasalazine-Model_1	Interact	-0.003		-1.114		0.003192	-0.00919
43	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Rhase	0.001	0.001	0.987		0.003064 0.264217	-0.00106 -0.00822
	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	0.128 -0.006	0.066 0.003	1.949 -1.952		0.264217	
44	Azathioprine-Model_3	TimePeriod	-0.00002175	0.001	-0.023	0.982	0.002042	-0.00209
45	Azathioprine-Model_3	Phase	0.161	0.053	3.059		0.270387	
46	Azathioprine-Model_3 Methotrexate-Model 4	Interact TimePeriod	-0.009 0.004	0.003 0.001	-3.398 5.374	<u>0.003</u> 0	-0.00281 0.006064	
47	Methotrexate-Model_4 Methotrexate-Model_4	Phase	-0.017		-0.509		0.008084	-0.08717
48	Methotrexate-Model_4	Interact	-0.001	0.002	-0.377	0.71	0.003128	
49	Leflunomide-Model_5	TimePeriod	0.004	0.001	4.722	0		0.001936
50	Leflunomide-Model_5 Leflunomide-Model 5	Phase Interact	-0.04 0	0.038 0.002	-1.044 0.058	0.309 0.954	0.038428 0.004128	-0.11843 -0.00413
			0					
51	ARIMA(0,0,1), MA, No Transformation	TimeP	Estimate	Standard Error		P-value		LCI
52	Sulfasalazine-Model_1 Sulfasalazine-Model 1	TimePeriod Phase	26528.53 44198.442	7721.626 489757.264	3.436 0.09	<u>0.003</u> 0.929	42465.18 1055008	10591.88 -966611
53	Sulfasalazine-Model_1	Interact	-29893.865	24000.178			19640.07	
54	Hydroxychloroquinesulfate-Model_2	TimePeriod	5769.508	5354.787	1.077		16821.25	
55	Hydroxychloroquinesulfate-Model_2	Phase	687248.921	320491.407	2.144	0.044		25787.17
56	Hydroxychloroquinesulfate-Model_2 Azathioprine-Model 3	Interact TimePeriod	-32332.165 83.53	14877.977 4192.71	-2.173 0.02	<u>0.042</u> 0.984	-1625.53 8736.858	-63038.8 -8569.8
	Azathioprine-Model_3	Phase	733233.954		3.007	0.007		230048.1
57	Azathioprine-Model_3	Interact	-39498.697	11810.828		0.003	-15122.3	-63875
58	Methotrexate-Model_4 Methotrexate-Model_4	TimePeriod Phase	16630.548 -80776.956	2992.036 140567.625	5.558		22805.81 209340.4	10455.29 -370894
59	Methotrexate-Model_4 Methotrexate-Model_4	Interact	-80776.956 -2192.432	6725.045			209340.4 11687.38	
60	Leflunomide-Model_5	TimePeriod	2041.806	432.517	4.721	<u>0.0001</u>	2934.477	1149.135
	Leflunomide-Model_5	Phase	-21148.135		-1.015		21846.06	-64142.3
	Leflunomide-Model_5	Interact	28.158	1010.937	0.028	0.978	2114.629	-2058.31

		BMJ Open	mjopen-2021-051936 on 23	Page 28 of 38
, Supplementary Table 3 -	- Ouantity & Cost		-202	
			-1-02	
2 3			5193	
4			8 0	
5			on 2	
6 Supplemental Results (Total Quantity)			3 D	
7 CHEMICAL_SUBSTANCE Jan-19 Feb-19 8 Sulfasalazine 9.54 8.61		Nov-19 Dec-19 Jan-20 Feb-20 Mar-20 Apr-20 May-20 Ju 9.23 9.32 9.79 8.64 10.26 9.45 8.94		an-21 Trend 9.38 ///////
OHydroxychloroquine sulfate4.894.37QAzathioprine4.694.24	7 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 4.46 4.52 4.45 4.11 4.81 4.90 4.52	4.77 4.91 4.41 4.78 4.84 4.66 5.02 4.56 4.54 4.09 4.42 4.44 4.27 4.62	4.68
10 effunomide 4.19 3.81 0 effunomide 0.56 0.50	1 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 0.55 0.56 0.56 0.51 0.60 0.57 0.53	4.227 4.40 3.98 4.29 4.33 4.18 4.55 0.54 0.56 0.52 0.56 0.57 0.55 0.59	4.17
1 Table 1 Total Quantity; Monthly Subtotal (in millions)	0.34 0.35 0.37 0.35 0.34 0.39 0.35 0.37	0.55 0.50 0.50 0.51 0.50 0.57 0.55	4.27 4.40 3.98 4.29 4.33 4.18 4.55 0.50 0.56 0.52 0.56 0.57 0.55 0.59	0.55 0.22 0.20
12			Do	
		v-19 Dec-19 Jan-20 Feb-20 Mar-20 Apr-20 May-20 Jun-2	0 SJul-20 Aug-20 Sep-20 Oct-20 Nov-20 Dec-20 Jan-2	
1 4ulfasalazine 0.62 0.56 1 bydroxychloroquine sulfate 0.30 0.27 1 5 zathioprine 0.19 0.17	7 0.29 0.28 0.39 0.49 0.45 0.45 0.38 0.37	0.62 0.62 0.65 0.58 0.68 0.61 0.57 0.35 0.36 0.54 0.50 0.62 0.77 0.55	0.40 0.51 0.46 0.50 0.54 0.53 0.56	0.81
16 ^{//ethotrexate} 3.27 3.12	7 0.18 0.20 0.21 0.19 0.20 0.23 0.21 0.22 2 3.45 3.43 3.73 3.52 3.75 4.01 3.85 4.15	0.21 0.22 0.32 0.20 0.56 0.59 0.47 4.02 4.21 4.29 3.96 4.70 4.47 4.26	0.4 0.27 0.24 0.26 0.24 0.23 0.24 4.4 4.67 4.33 4.65 4.68 4.56 4.94	0.25
Leflunomide 0.12 0.10 17Table 2 Actual Cost; Monthly Subtotal (in £millions) 0.10 0.10	0 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	0.11 0.10 0.10 0.10 0.09 0.10	0.09
18			n ht	
19				
20				
21 22			jope	
23			n.b	
24			and the second sec	
25			Š.	
26 27				
27 28			Ap	
29			rii 2	
30		0.21 0.22 0.32 0.20 0.56 0.59 0.47 4.02 4.21 4.29 3.96 4.70 4.47 4.26 0.12 0.12 0.12 0.11 0.12 0.10 0.10	ο. Ν	
31			024	
32 33			. by	
34			gue	
35			ist.	
36			Prot	
37			lect	
38			ed t	
39 40			0.10 0.10 0.10 0.10 0.10 0.09 0.10 110 0.10 0.10 0.10 0.10 0.10 0.09 0.10 110 0.10 0.10 0.10 0.10 0.10 0.10 0.10 110 0.10 0.10 0.10 0.10 0.10 0.10 0.10	
40			ору	
42			righ	
43	For peer review only - http://bm	jopen.bmj.com/site/about/guidelines.xhtml	Ŧ	
44		eperment, ste, asour, guarmes, httm		
45				

mjopen-2021-051936 on 23 1 2 3 4 5 6 Aug-19 Sec.20 Total Quantity by region Jan-19 Feb-19 Mar-19 Apr-19 Mav-19 Jun-19 Jul-19 Sep-19 Oct-19 Nov-19 Dec-19 Jan-20 Feb-20 Mar-20 Apr-20 Mav-20 Jun-20 Jul-20 Aug-20 Oct-20 Nov-20 Dec-20 Jan-21 Trend lecem 7 North West + North East and Yorkshire, 6.2 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 6.68 6.66 6.43 7.01 6.54 mm Midlands + East of England, 7.77 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 mm 7. 8 South East + South West 6.65 6.33 6.27 6.71 6.44 6.53 6.61 7.17 6.84 6.35 6.42 6.61 5.98 6.49 6.5 mm 6.5 6.79 6.32 6.9 6.36 6. 6.46 6.35 6.88 6. 0 2.49 9 London UNIDENTIFIED 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 2.54 2.4 2.6 2.47 mm 0 0 0. 0 0. 0 0 0 0 0.01 0. _____ 0. 0 0. 0 0. 0 0. 0. 0 0. 0. 0. 0. 23.08 1 Olonthly Subtotal Table 3 Total Quantity in millions by region 23.1 23.84 21.52 **▶**^{23.23} 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 23.25 22.54 24.52 11 Sep-20 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 Oct-20 Nov-20 Dec-20 Jan-21 Trend t-test (North vs. Total) 12 Jorth West + North East and Yorkshire, 0.8 ------1.11 1.03 1.12 1.12 1.23 1.2 1.24 1.33 1.25 1.32 1.25 1.4 1.25 1.57 1.53 1.39 1.42 0.82 0.74 $\nabla^{0.79}$ 0.79 0.77 0.84 9.99E-35 1.3 P-value

 1.98
 205

 0.25
 0.25

 5.51
 5.52

 2.23 0 2.17 2.26 0.31 1 South East + South West 2.01 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 2.17 2.16 2.31 2.33 -----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 2.32 2.26 2.48 0.33 ------0.22 0.2 0.22 0.22 0.25 0.26 0.27 0.26 0.32 0.31 0.33 0 0 0 0 0 0 0 0 0 0 0 15^{Monthly Subtotal} Table 4 Actual Cost in £millions by region 4.51 4.23 4.64 4.62 5.09 4.91 5.11 5.47 5.54 5.59 5.5 5.96 5.68 ed from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 29 of 38

44 45 46

Supplementary Table 4 - Region

Sunn	lementarv	/ Table 5 -	Methotrexate	Quantity (in	millions)
Sabb	i ci i ci i cui j		Wie thou chate	Quantity (

May-19

4.05 4.064 0.064 0.064 0.043 0.043 0.043 0.02 0.02 0.02 0.011 0.011 0.011 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.000 0.002 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.001 0.002 0.001 0.002 0.001 0.001 0.002 0.002 0.001 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 0.001 0.001 0.001 0.001 0.001 0.001 0.0007 0.007 0.007 0.007 0.007 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.001 0.001 0.001 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.0000 0.0

0. 0.001 0.001 0.001

0.001

0.009 0.012 0.006

0.006 0.006 0.006 0.009 0.006 0.006 0.006 0.002 0.001 0.001 0.001

0. 0.001 0.001 0.001 0

0.001 0.001 0.001 0.001

n-19 3.928 0.055 0.055 0.037 0.037

0.036 0.036 0.016 0.035 0.01 0.035 0.01 0.008 0.008 0.008 0.003 0.005

0.005 0.005 0.006 0.006

0.000 0.006 0.006 0.003 0.001 0.001 0.003

0.

0. 0.001 0.001 0.001

Sum Total (Methotrexate)

Sum of top ten rows (10010: % Sum of top ten rows

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

4.253 97% 3.868 97% 4.187 4.116 97% 4.402 97% 4.061 97% 4.197 4.484 97% 4.143 97% 4.415 97% 4.228 97% 4.37 97% 4.374 97% 4.001 97% 4.662 97% 4.378 97% 4.187 97% 4.332 97% 4.52 97% 4.098 97% 4.416 97%

eb-19 ar-19

3.556 0.053 0.053 0.036 0.035 0.035 0.017 0.017 0.017 0.031 0.009 0.009 0.009 0.009 0.009 0.009

0.005 0.005 0.005 0.009 0.006 0.005 0.003 0.001 0.001 0.001 0.001 0.002

0.001 0.001 0.001

0.001

0.059 0.041 0.041 0.04 0.04 0.04 0.018 0.058 0.04 0.04 0.04 0.04 0.017 0.017

0.018 0.032 0.01 0.01 0.009 0.017 0.03 0.011 0.011 0.009

0.006 0.006 0.006

0.006

0.001 0.003

0. 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001 0.001

0.001

BNF CODE

BMJ Open

Oct-19

0.067 0.067 0.048 0.048 0.044 0.044 0.021 0.021 0.021 0.012 0.012 0.012 0.012 0.006 0.006 0.007 0.008 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005

0.072 0.072 0.051 0.051 0.049 0.049 0.022 0.022

0.028 0.012 0.012 0.011 0.011 0.012 0.007

0.007 0.007 0.008 0.008

0.009

0.006 0.005 0.002

0.001 0.001 0.002 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. 0.001 0.001 0.001 0.001

Nov-19

3.826 0.07 0.05 0.05 0.045 0.045 0.045 0.022

0.026 0.013 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.008 0.005 0.005 0.003 0.001 0.001

c-19
3.948
0.074
0.074
0.074
0.074
0.074
0.054
0.054
0.022
0.022
0.022
0.022
0.022
0.022
0.022
0.022
0.023
0.026
0.013
0.013
0.013
0.011
0.011
0.011
0.011
0.011
0.011
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
0.001
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
0.001
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
0.001
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

0.001 0.001 0.001 0.001 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001 0.001 0.001

0.001 0.001 0. 0.001 0.001 0.001 0.001

-20 3.949 0.075 0.075 0.053 0.048 0.048 0.023 0.023 0.023 0.023 0.023 0.023 0.013 0.011 0.011 0.011 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.015 0.015 0.015 0.015 0.053 0.048 0.023 0.023 0.013 0.011 0.011 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.05

0.07 0.07

0.049 0.049 0.046 0.021 0.021 0.022 0.012 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.002 0.001 0.002

0. 0.001 0.001 0.001 0

0. 0.001

0. 0.001 0.001 0.001 0.001

Jg-19

0.065 0.065 0.045 0.045 0.045 0.044 0.044 0.022 0.022 0.022 0.022 0.011 0.011 0.011 0.011 0.011 0.011 0.010 0.006 0.007 0.007 0.007 0.007 0.007 0.002 0.001 0.001 0.003 0.001 0.003 0.001

0. 0.001 0.001 0.001

0.001

0.069 0.048 0.046 0.046 0.046 0.021 0.021 0.013 0.01 0.013 0.007 0.009 0.006 0.005 0.005 0.002 0.001 0.001 0.001 0.001

0.001 0.001 0.001 0. 0.001 0.001 0.001

0.001 0.001

0.001

0.06 0.042 0.042 0.04 0.04 0.019 0.029 0.011 0.009 0.009 0.009 0.000 0.006 0.006 0.006 0.006 0.006 0.006 0.000 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001

r-20 3.934 0.079 0.079 0.056 0.056 0.052 0.052 0.023 0.023

0.023 0.014 0.014 0.012 0.012 0.012 0.012 0.009 0.009 0.009 0.008 0.008 0.008 0.008 0.008 0.008 0.005 0.005 0.005 0.002 0.002 0.002 0.002 0.002

0.001

0.001 0.001 0.001 0.001

4.195 0.083 0.066 0.054 0.055 0.025 0.025 0.025 0.025 0.015 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.009 0.008 0.008 0.008 0.008 0.000 0.003 0.002 0.002 0.002

0. 0.001 0.001 0.001 0 0. 0.001 0.001 0.001 0.

0.001

0.001 0.001 0.001 0.001 0.001

3.763 0.076 0.054 0.054 0.049 0.049 0.049 0.023 0.023

0.021 0.013 0.013 0.011 0.011 0.011 0.011

0.008 0.007 0.007

0.001 0.001 0.001 0.001 0.001 0.001

0.001

0. 0.001 0.001 0.001

3.89 0.078 0.056 0.056 0.052 0.052 0.023 0.023 0.023 0.022 0.014 0.014 0.012 0.012 0.012

0.008 0.008 0.008 0.007 0.005 0.004 0.003 0.002 0.002 0.002 0.002 0.001 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

UK-20 3.67 0.077 0.077 0.077 0.077 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.022 0.022 0.019 0.022 0.019 0.022 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.02 0.0

0.001 0.001 0.001 0.001 0.001 0.001

3.958 0.082 0.082 0.082 0.066 0.066 0.054 0.054 0.054 0.024 0.029 0.015 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.003 0.009 0.009 0.0002 0.002 0.002

0.001 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

0.084 0.084 0.06 0.056 0.0256 0.024 0.024 0.024 0.019 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.013 0.009 0.008 0.009 0.009 0.008 0.000 0.000 0.002 0.002 0.002 0.002 0.001 0.001 0.001 0.001 0.001 0.001

Sup
1
2
3 4 5
5
6
7 BNF DESCRIPTION Methotrexate 5mg/2ml solution for injection vials Methotrexate 50mg/2ml solution for injection vials
Methotrexate 22.5mg/0.9ml inj pre-filled syringes
1 Dethotrexate 7.5mg/0.3ml inj pre-filled syringes
Methotrexate 12.5mg/0.5ml inj pre-filled syringes Methotrexate 15mg/0.6ml inj pre-filled syringes Methotrexate 17.5mg/0.7ml inj pre-filled syringes
1 2 Methotrexate 7.5mg/0.5ml inj pre-filled disposable Methotrexate 10mg/0.4ml inj pre-filled disposable Methotrexate 12.5mg/0.5ml inj pre-filled disposable
Stethotrexate 15mg/0.6ml inj pre-filled disposable Methotrexate 17.5mg/0.7ml inj pre-filled disposable Methotrexate 20mg/0.8ml inj pre-filled disposable
4 ethotrexate 22.5mg/0.9ml inj pre-filled disposabl Methotrexate 25mg/1ml inj pre-filled disposable de Catal 20mg/0.8ml solution for injection pre-fille
Jatal 20mg/0.8ml solution for injection pre-fille Jatal 22.5mg/0.9ml inj pre-filled syringes Zlatal 25mg/1ml solution for injection pre-filled Jatal 10mg/0.4ml solution for injection pre-fille Zlatal 7.5mg/0.3ml inj pre-filled syringes
1 Zatal 12.5mg/0.5ml inj pre-filled syringes Zatal 15mg/0.6ml solution for injection pre-fille
Zlatal 17.5mg/0.7ml inj pre-filled syringes ordimet 7.5mg/0.3ml solution for injection pre-fi Nordimet 10mg/0.4ml solution for injection pre-fil
1 Oprimet 12.5mg/0.5ml solution for injection pre-fl Nordimet 15mg/0.6ml solution for injection pre-fil Nordimet 17.5mg/0.7ml solution for injection pre-fil
20 ordimet 20mg/0.8ml solution for injection pre-fil Nordimet 20.5mg/0.9ml solution for injection pre-fil Nordimet 25.5mg/1.9ml solution for injection pre-file
2 Methotrexate 2.5mg tablets 2 Methotrexate 2.5mg/5ml oral liquid
Methotrexate 5mg/5ml oral liquid 2 Methotrexate 10mg/5ml oral liquid Methotrexate 7.5mg/5ml oral liquid
4 Methotrexate 12.5mg/5ml oral liquid 4 Methotrexate 15mg/5ml oral liquid Methotrexate 20mg/2ml inj pre-filled syringes
2 Stethotrexate 15mg/1.5ml inj pre-filled syringes Methotrexate 7.5mg/0.15ml inj pre-filled syringes Methotrexate 10mg/0.2ml inj pre-filled syringes
2 methottexate 12mg/0.3ml inj pre-filed syringes Methotrexate 22mg/0.3ml inj pre-filed syringes Methotrexate 22mg/0.4ml inj pre-filed syringes 2 methotrexate 25mg/0.5ml inj pre-filed syringes
2 Methotrexate 30mg/0.6ml inj pre-tilled syringes 28 Methotrexate 12.5mg/0.25ml inj pre-filled syringes Methotrexate 17.5mg/0.35ml inj pre-filled syringes Methotrexate 22.5mg/0.45ml inj pre-filled syringes
2 Dethotrexate 17.5mg/0.35ml inj pre-filled disposab Methotrexate 20mg/0.4ml inj pre-filled disposable
Methotrexate 22.5mg/0.45ml inj pre-filled disposab Methotrexate 7.5mg/0.15ml inj pre-filled disposab Methotrexate 27.5mg/0.55ml inj pre-filled disposab
3 Nethotrexate 30mg/0.5ml inj pre-filled disposable Methotrexate 25mg/0.5ml inj pre-filled disposable Methotrexate 15mg/0.3ml inj pre-filled disposable 2 Dethotrexate 12.5mg/0.25ml inj pre-filled disposab
Methotrexate 10.mg/0.2ml inj pre-filled disposable 3 Sitehotrexate 2mg/ml oral solution sugar free Sitehotrexate 2.5mg tablets
Maxtrex 10mg tablets 4 etoject 20mg/2ml solution for injection pre-fille Metoject 10mg/1ml solution for injection pre-fille
3 Statolect 15mg/1.5ml inj pre-filled syringes
3 decipient 7.5mg/0.15ml inj pre-filled syringes detoject 10mg/0.2ml inj pre-filled syringes Metoject 10mg/0.2ml inj pre-filled syringes 7 the toiect 20mg/0.4ml inj pre-filled syringes
 Tetoject 20mg/0.4ml inj pre-filled syringes Metoject 25mg/0.5ml inj pre-filled syringes Metoject 12.5mg/0.25ml inj pre-filled syringes Metoject 22.5mg/0.45ml inj pre-filled syringes
Metoject 22.5mg/0.45ml inj pre-filled syringes Qetoject PEN 17.5mg/0.35ml inj pre-filled pens Metoject PEN 17.5mg/0.35ml inj pre-filled pen
Metoject PEN 20mg/0.4ml inj pre-filled pens detoject PEN 20mg/0.4ml inj pre-filled pen Metoject PEN 22.5mg/0.45ml inj pre-filled pens
4 Metoject PEN 22.5mg/0.45ml inj pre-filled pen Metoject PEN 7.5mg/0.15ml inj pre-filled pen Metoject PEN 7.5mg/0.15ml inj pre-filled pens
4 Zhetoject PEN 27.5mg/0.55ml inj pre-filled pens Metoject PEN 27.5mg/0.55ml inj pre-filled pen
4 3 letoject PEN 30mg/0.6ml inj pre-filled pens Metoject PEN 30mg/0.6ml inj pre-filled pen Metoject PEN 25mg/0.5ml inj pre-filled pen
Metoject PEN 15mg/0.3ml inj pre-filled pen 4 Snetoject PEN 15mg/0.3ml inj pre-filled pens Snetoject PEN 12.5mg/0.25ml inj pre-filled pens
4 Metoject PEN 10mg/0.2ml inj pre-filled pens
Metoject PEN 10mg/0.2ml inj pre-filled pen 4 Metofill 7.5mg/0.15ml inj pre-filled injector Methofill 10mg/0.2ml inj pre-filled injector Methofill 12.5mg/0.25ml inj pre-filled injector
Aethofill 12.5mg/0.25ml inj pre-filled injector dethofill 15mg/0.3ml inj pre-filled injector Methofill 17.5mg/0.35ml inj pre-filled injector dethofill 20mg/0.4ml inj pre-filled injector
Methofill 25mg/0.5ml inj pre-filled injector 6 Methofill 27.5mg/0.55ml inj pre-filled injector
5 thethofill 10mg/0.2ml inj pre-filled syringes
5 Prethofill 17.5mg/0.35ml inj pre-filled syringes
Methofill 22.5mg/0.45ml inj pre-filled syringes 5 Shethofill 25mg/0.5ml inj pre-filled syringes 12.5mg/0.25ml inj pre-filled syringes
54 55
56
57
50

- 59
- 60

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

v-20

0.081 0.059 0.059 0.053 0.053 0.053 0.023

0.017 0.014 0.014 0.013 0.013 0.009 0.009 0.008 0.008 0.008 0.008 0.008 0.004 0.004 0.004 0.004 0.002 0.002

0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001

0.064 0.064 0.058 0.058 0.025 0.025

0.02 0.016 0.016 0.014 0.014 0.014 0.011 0.009

0.009

0.004 0.004 0.003 0.002

0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001

4.68 97% 4.299 97%

4.459 97% 4.299 97% 18-14 18-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items 01 01 01 01 01 01 01 01 01 01 01 01 01 0	Location in manuscript where items are reported
Title and abstr	act			Decer	
	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 		RECORD 1.1: The type of stata used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title and abstrac PG 2
		summary of what was done and what was found	Pr rela	RECORD 1.2: If applicable, the geographic region and stimeframe within which the study took place should be reported in the title or abstract.	Title and abstrac PG 2
			6	RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	N/A
Introduction				n April 23,	
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		23, 2024 by gue	In Introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses		st. Protected by copyright.	End of Introduction section (pg 5)
Methods				у сору	
		For peer review only - ht	tp://hmiopen.hmi.com/site	29 Trig /about/quidelines.vhtml	

 31 of 38
 BMJ Open
 <td

 Page 32 of 38

			BMJ Open	36/bmjo	Page 32
Study Design	4	Present key elements of study design early in the paper		pen-2021-051	Materials and methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		936 on 23 Decemb	Materials and methods section
	-	A Contraction		er 2022	
Participants	6	 (a) Cohort study- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study-</i> 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 <i>Cross-sectional</i> <i>study-</i> 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.	Materials and methods section

BMIOnen

Page 33 of	f 38			BMJ Open	36/bmjop	
1 2 3 4 5			<i>Case-control study-</i> For matched studies, give matching criteria and the number of controls per case		en-2021-051936	
-	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete fist of codes and algorithms used by 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)
22	Data sources/ neasurement	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	evie	://bmjopen.bmj.com/ on April 23, 2024 by g	Materials and methods section. Original data are available from <u>https://www.nhsbs</u> <u>a.nhs.uk/prescripti</u> <u>on- data/prescribing- data/english- prescribing-data- epd</u>
36 37					Juest	
40 41	Bias	9	Describe any efforts to address potential sources of bias		Protected by copyright	N/A
42 43 44 45 46			For peer review only - htt	:p://bmjopen.bmj.com/site/		

			BMJ Open	36/bmjop	Page
Study size	10	Explain how the study size was arrived at		pen-2021-	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		051936 on 23 Decer	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 		nber 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by gu	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

Page 3	5 of 38			BMJ Open	36/bmjopen-2			
2 3 4 5 6 7					RECORD 12.2: Authors should provide information on the data cleaning methods used by the study.	Materials and methods section		
8 9 10 11 12 13 14 15 16	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.		
17 18 19	Results			24	d from			
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, 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 	revie	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , 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		
			For peer review only - ht [,]	tp://bmjopen.bmj.com/site/	y guest. Protected by copyright. /about/guidelines.xhtml			

			BMJ Open		36/bmjop	Page 36	6 of 38
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) <i>Cohort study</i>- summarise follow-up time (e.g., average and total amount) 			Φ	Results, Table 1	
Outcome data	15	<i>Cohort study-</i> Report numbers of outcome events or summary measures over time <i>Case-control study-</i> Report numbers in each exposure			ownloaded from http://bmj	Results, Table 1	
			· Vio		open.br		_
		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		201/2	nj.com/ on April 23,		
		For peer review only - htt	tp://bmjopen.bmj.com/site/	e/about/guidelines.xhtml	2024 by guest. Protected by copyright.		

Page 3	7 of 38	36/bmio					
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28	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 			36/bmioden-2021-051936 on 23 December 2022. Downloaded frbm http://bmiopen.bmi.com/ on April 23	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	revie	200	om http://bmiopen.bmi.com/ on A	Results section. Supplementary - ARIMA Syntax Supplementary - Sensitivity analysis
29 30 31	Discussion	•				April 23	
32 33 34 35	Key results	18	Summarise key results with reference to study objectives			. 2024 by gu	Discussion section
36 37 38 39 40 41 42 43 44 45 46 47			For peer review only - ht	tp://bmjopen.bmj.com/site,	/about/guidelines.xhtml	est. Protected by copyright.	

			BMJ Open	36/bmjoj	Page
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 not created or collected to ans specific research question(3). I discussion of misclassification unmeasured confounding, misc data, and changing eligibility of time, as they pertain to the stud being reported.	wer the nclude bias, sing over
Interpretation	20	Give a cautious overall interpretation of results considering objectives,		2022. Down	Discussion section
		D _R		oa ded t	
		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	r rev:	rom http://bmjop	
Generalisability	21	Discuss the generalisability (external validity) of the study results	0	en.bmj.com/	Discussion section
Other Informati	on	•		Apri	
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		123, 2024	Acknowledgment section
		·	<u>.</u>	by guest. Protected by copyright	i
		For peer review only - htt	tp://bmjopen.bmj.com/site	/about/guidelines.xhtml	

Page 39 c	of 38		BMJ Open	36/bmjo		
2 3 4 5 6 7	Accessibility of protocol, raw data, and programming code			RECORD 22.1: Authors sho provide information on how access any supplemental information such as the stud protocol, raw data, or progra code.	to ly	Supplementary ARIMA Syntax Supplementary Sensitivity analysis
12 Co 13 in 14	ommittee. The REp press.	porting		ted health Data (RECORD) S2. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.	atement. <i>PL</i>	

BMJ Open

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 s You must view these files (e.g.	submitted by the author for peer review, but cannot be converted to PDF movies) online.					
25 November 2022 at 17_24_51_default_f4b41e4e.mp4						

SCHOLARONE[™] Manuscripts



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 <u>licence</u>.

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 <u>Creative Commons</u> 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.

relievon

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:

- Mrs. Ravina Barrett (<u>https://orcid.org/0000-0003-0004-2131</u>) 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, <u>R.Barrett2@Brighton.ac.uk</u>
- 2. Mr. Robert Barrett, MBA, MCSE, MCSA, MCP, ITIL, Prince 2 <u>rob-barrett@outlook.com</u>; <u>https://orcid.org/0000-0003-3402-3377</u> 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, <u>X.Lin@soton.ac.uk</u>
- 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, <u>d.j.culliford@soton.ac.uk</u>
- 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 (<u>https://orcid.org/</u>) <u>S.Fraser@soton.ac.uk</u>.
- 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, <u>cedwards@soton.ac.uk</u>

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, pvalue = 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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 Qu	uantity	Actual Cost (£)	
Medicine	Mean	SD	UCI	LCI	Mean	SD	UCI	LCI	Mean	SD	Mean	SD
Sulfasalazine Hydroxychloroquine	9.303	0.384	9.504	9.102	9.267	0.468	9.544	8.991	9.28	0.422	0.628	0.039
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:

- 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.
- 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.
- 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.
- 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 antirheumatics 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.

Estimated slope (per month) BEFORE March 2020	Parameter Estimate	Standard Error	T-statistic	P-value	Lower Cl	Upper Cl	
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	

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

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] <u>https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd.</u> 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.

L'EZ ONI

References

- 1 NHS services. Who can get free prescriptions. nhs.uk. 2020.https://www.nhs.uk/nhsservices/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/healthand wellbeing/articles/nhs70marking70yearsofthenationalhealthservice/2018-06-26 (accessed 12 Oct 2022).
- 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-usesof-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-lessonslearned-to-date-report-government-response/the-governments-response-to-the-health-andsocial-care-committee-and-science-and-technology-committee-joint-report-coronaviruslessons-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_documentsupply_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

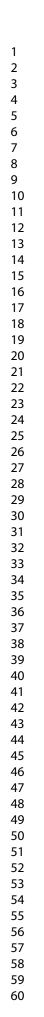
- 60 Osamor K. I warned parliament that NHS 111 would never be able to cope. The Guardian. 2020.https://www.theguardian.com/commentisfree/2020/apr/23/nhs-111-crisis-coronavirus-pandemic (accessed 9 Jun 2020).
- 61 Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2016;:dyw098. doi:10.1093/ije/dyw098
- 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

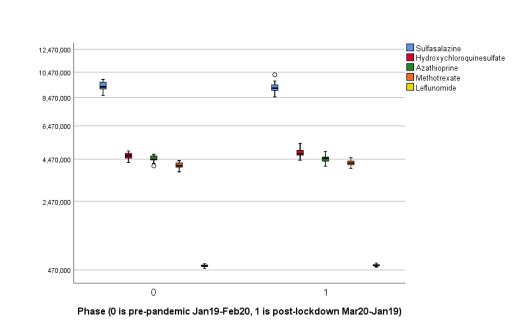
FIGURE TITLES AND LEGENDS

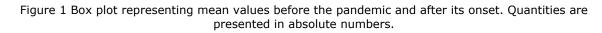
Figure 1. Box plot representing mean values before the pandemic and after its onset Quantities are presented in absolute numbers.

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)







300x176mm (72 x 72 DPI)

60

- Observed

Sulfasalazine-Model_

Hydroxychloroquinesulfate-Model_2

'N

Azathioprine-Model

Ċ,

Methotrexate-Model

ь.

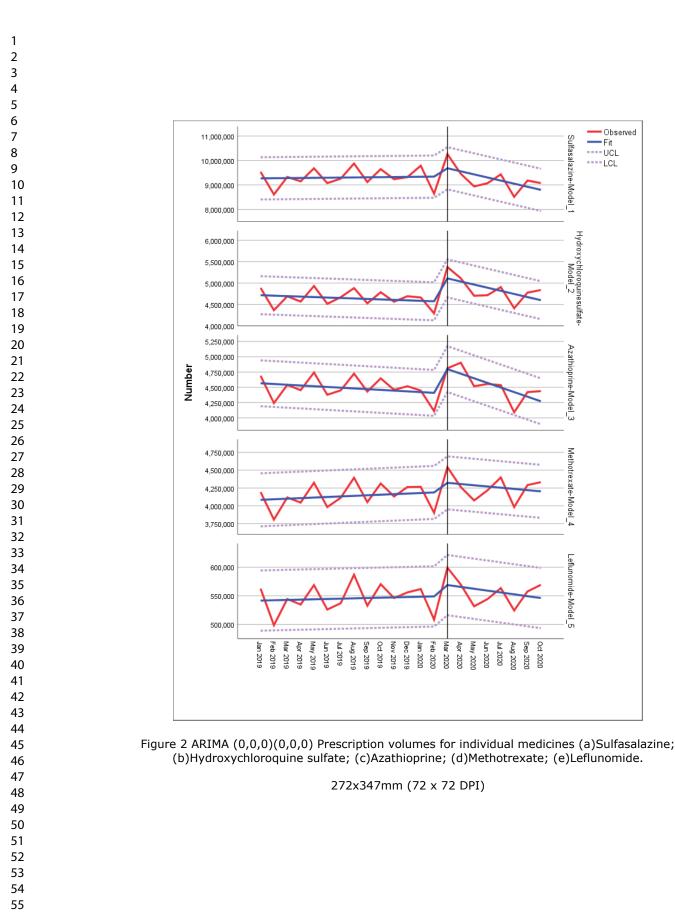
Leflunomide-Model

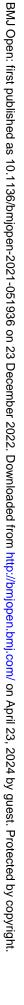
σī

Aug 2020 Sep 2020 Oct 2020 _ Fit

----UCL

----LCL







BMJ Open: first published as 10.1136/bmjopen-2021-051936 on 23 December 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

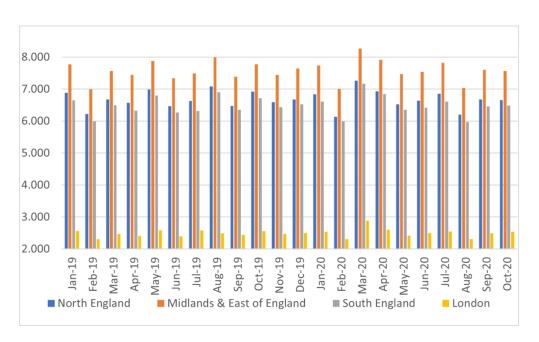


Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of RA medicines are presented in the callouts).

127x76mm (330 x 330 DPI)

Page 23 of 44 Supplementary Table 1 - ARIMA Syntax (Mar20-1) Jan 19 to Jan 21

2	
3	* Encoding: UTF-8.
4	
5	
6	DATASET ACTIVATE DataSet3.
7	PREDICT THRU END.
8	* Time Series Modeler.
9	TSMODEL
10	/MODELSUMMARY PRINT=[MODELFIT]
11	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
12	/MODELDETAILS PRINT=[PARAMETERS]
13	SERIESPLOT OBSERVED FIT FORECASTCI FITCI
14	/OUTPUTFILTER DISPLAY=ALLMODELS
15	/SAVE PREDICTED(Predicted) LCL(LCL) UCL(UCL)
16 17	/AUXILIARY_CILEVEL=95 MAXACFLAGS=24
18	
19	/MISSING USERMISSING=EXCLUDE
20	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
21	e
22	INDEPENDENT=TimePeriod Phase Interact
23	PREFIX='Model'
24	/ARIMA AR=[1] DIFF=0 MA=[0]
25	TRANSFORM=NONE CONSTANT=YES
26	AUTOOUTLIER DETECT=OFF.
27	
28	PREDICT THRU END.
29	* Time Series Modeler.
30	TSMODEL
31	/MODELSUMMARY PRINT=[MODELFIT]
32	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
33	
34	/MODELDETAILS PRINT=[PARAMETERS]
35	
36 37	/OUTPUTFILTER DISPLAY=ALLMODELS
38	/SAVE PREDICTED(Predicted) LCL(LCL) UCL(UCL)
39	AUXILIARY CILEVEL=95 MAXACFLAGS=24
40	/MISSING USERMISSING=EXCLUDE
41	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
42	e
43	INDEPENDENT=TimePeriod Phase Interact
44	PREFIX='Model'
45	/ARIMA AR=[0] DIFF=1 MA=[0]
46	TRANSFORM=NONE CONSTANT=YES
47	AUTOOUTLIER DETECT=OFF.
48	
49	PREDICT THRU END.
50	* Time Series Modeler.
51	
52	
53 54	/MODELSUMMARY PRINT=[MODELFIT]
54 55	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
55 56	/MODELDETAILS PRINT=[PARAMETERS]
57	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
58	/OUTPUTFILTER DISPLAY=ALLMODELS
59	AUXILIARY CILEVEL=95 MAXACFLAGS=24
60	/MISSING USERMISSING=EXCLUDE

BMJ Open

2	
3	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
4	e
5	INDEPENDENT=TimePeriod Phase Interact
6	
7	PREFIX='Model'
8	/ARIMA AR=[0] DIFF=0 MA=[1]
9	TRANSFORM=NONE CONSTANT=YES
10	/AUTOOUTLIER DETECT=OFF.
11	
12	PREDICT THRU END.
13	
14	* Time Series Modeler.
15	TSMODEL
16	/MODELSUMMARY PRINT=[MODELFIT]
17	/MODELSTATISTICS DISPLAY=YES MODELFIT=[SRSQUARE]
18	/MODELDETAILS PRINT=[PARAMETERS]
19	/SERIESPLOT OBSERVED FIT FORECASTCI FITCI
20	/OUTPUTFILTER DISPLAY=ALLMODELS
21	AUXILIARY CILEVEL=95 MAXACFLAGS=24
22	
23	/MISSING USERMISSING=EXCLUDE
24	/MODEL DEPENDENT=Sulfasalazine Hydroxychloroquinesulfate Azathioprine Methotrexate Leflunor
25	e
26	INDEPENDENT=TimePeriod Phase Interact
27	PREFIX='Model'
28	/ARIMA AR=[0] DIFF=0 MA=[0]
29	TRANSFORM=LN CONSTANT=YES
30	TRANSFORM-LIN CONSTANT-TES
31	/AUTOOUTLIER DETECT=OFF.
32	/AUTOOUTLIER DETECT=OFF.
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
52	
55	
55	
55	
57	
58	
58 59	
60	
00	

BMJ Open

1	ARIMA Model Parameters	ARIMA (March20+ is a '1')	Total Quanti	ties					
2 3 -					0) before th	e COVID-19	first lockd	own in Englar	nd (23rd Mar-20) until 11 months after this date (Mar-20 to Jan-21)
4	ARIMA(0,0,0), No Transformation	TimePeriod (Before); Phase (Step); Interact (After)	Estimate					.CI	
5	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	5435 659017	28871 875894	0.188	0.852 0.46	65021 2466774	-54151 -1148740	Confidence intervals were calculated as (24df): Cl=parameter+/-tinv(0.05, df)*SE
	ulfasalazine-Model_1	Interact	-38151		-0.754	0.459	66220	-142522	
	Hydroxychloroquinesulfate-Model_2	TimePeriod	-10955		-0.764	0.453	18632	-40543	
	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	814729 -24392		1.873 -0.971	0.075	1712394 27434	-82935 -76219	
U /	Azathioprine-Model_3	TimePeriod	-12052		-0.982	0.337	13278	-37382	
	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	786705 -31340		2.113 -1.458	<u>0.047</u> 0.16	<u>1555182</u> 13028	<u>18229</u> - 75708	
10	Vethotrexate-Model 4	TimePeriod	-51340		0.673	0.18	32395	-16462	
11	Methotrexate-Model_4	Phase	249614		0.695	0.495	990758	-491531	
1	Methotrexate-Model_4 .eflunomide-Model_5	Interact TimePeriod	-10634 561		-0.513 0.338	0.613 0.739	32156 3992	-53424 -2870	
	eflunomide-Model 5	Phase	30388		0.603	0.553	134482	-73706	
13	eflunomide-Model_5	Interact	-1188	2912	-0.408	0.687	4822	-7198	
14-									
15		TimePeriod (Before); Phase	Parameter						
	ARIMA(1,0,0), AR	(Step); Interact (After)	Estimate	Standard Erro 20233				-21999	
	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	19759 417103		0.977	0.34 0.505	61517 1686169	-21999	the coefficient for 'time' gives us the slope of the regression line pre-intervention the coefficient for 'phase' gives us the change in intercept
17	sulfasalazine-Model_1 sulfasalazine-Model_1	Interact	-37930	34973	-1.085	0.291	34250	-110110	the coefficient for 'interact' gives us the change in slope post intervention
18	Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	-5175		-0.469	0.644	17613	-27962	If the coefficient for time is R1 for phase is R2 and for interact is R2 than the correction and the
	Hydroxychloroquinesulfate-Model_2	Phase Interact	700712 -23233		2.087 -1.216	0.05 0.238	1393748 16188	7675 -62654	If the coefficient for time is β 1, for phase is β 2 and for interact is β 3 then the regression model is:
	Azathioprine-Model 3	TimePeriod	-9123	10465	-0.872	0.394	12476	-30722	Therefore, pre intervention becomes:
	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	738472 -31213		2.326 -1.73	<u>0.031</u> 0.099	<u>1393704</u> 6021	<u>83240</u> -68447	Outcome = constant + β1time
217	Vethotrexate-Model 4	TimePeriod	-51215		1.963	0.099	28852	-08447	
- 22	viethotrexate-iviouei_4	Phase	86932	218834	0.397	0.695	538582	-364718	Outcome = constant + β 1time + β 2 + β 3interact = (constant + β 2) + (β 1 + β 3) time
1	Methotrexate-Model_4 .eflunomide-Model_5	Interact TimePeriod	-7128 1432		-0.575 1.295	0.572 0.21	18463 3714	-32718 -850	(as time and interact are the same post intervention)
	oflunomido Model 5	Phase	11071	33718	0.328	0.746	80661	-58520	
24	eflunomide-Model_5	Interact	-882	1912	-0.461	0.649	3063	-4827	
25-					$ \mathbf{A} $				
26		TimePeriod (Before); Phase	Parameter						
	ARIMA(0,1,0), Difference	(Step); Interact (After)	Estimate	Standard Erro	-0.304			.CI	
	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod Phase	-16503 446642		-0.304	0.764	95395 3524086	-128402 -2630801	
28	Sulfasalazine-Model_1 Sulfasalazine-Model_1	Interact	-5626	88335	-0.064	0.95	176688	-187940	
29	Hydroxychloroquinesulfate-Model_2	TimePeriod	-4262 712710		-0.146	0.886	56059	-64583	
30	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	-29016		0.887	0.386 0.549	2371664 69263	-946244 -127296	
4	zathionrine-Model 3	TimePeriod	-6734	23232	-0.29	0.775	41214	-54683	
31/	Azathioprine-Model_3	Phase	573262 -21531		0.897 -0.569	0.38 0.576	1891942 56590	-745419 -99652	
32	Azathioprine-Model_3 Methotrexate-Model_4	Interact TimePeriod	-21331 -6809		-0.292	0.378	41292	-54909	
33	Methotrexate-Model_4	Phase	439338		0.685	0.501	1762190	-883514	
	Methotrexate-Model_4 .eflunomide-Model_5	Interact TimePeriod	-15532 -753		-0.409	0.687 0.816	62837 5828	-93900 -7333	
		Phase	58732		0.67	0.510	239712	-122249	
35	.eflunomide-Model_5 .eflunomide-Model_5	Interact	-2093	5195	-0.403	0.691	8629	-12814	
36-									
37		TimePeriod (Before); Phase	Parameter						
4	ARIMA(0,0,1), MA Sulfasalazine-Model_1	(Step); Interact (After)		Standard Erro 9982		P-value 0.011	48437	.CI	
		TimePeriod Phase	27834 459301		2.788 1.091	0.288	<u>48437</u> 1328214	7231 -409613	
39	sulfasalazine-Model_1 sulfasalazine-Model_1	Interact	-50867	21544	-2.361	<u>0.028</u>	<u>-6402</u>	<u>-95332</u>	
40		TimePeriod Phase	1157 637368		0.223 3.065	0.826 0.006	11859 1066559	-9545 <u>208178</u>	
	lydroxychloroquinesulfate-Model_2	Interact	-26929		-2.51	0.006	<u>-4783</u>	-49075	
	vathionrine-Model 3	TimePeriod	-2278	4740	-0.481	0.636	7505	-12062	
42/	Azathioprine-Model_3 Azathioprine-Model_3	Phase Interact	660176 -34495		3.93 -3.873	0.001 0.001	<u>1006868</u> <u>-16113</u>	<u>313483</u> -52878	
43	Azathioprine-Model_3 Methotrexate-Model_4	TimePeriod	18549	3714	4.994	0.00007	26214	<u>10884</u>	
	Methotrexate-Model_4 Methotrexate-Model_4	Phase	27587 -8773		0.236 -1.499	0.816 0.149	268434 3304	-213260 -20850	
45	eflunomide-Model_5	Interact TimePeriod	2037		3.754	0.149 0.001	<u>3304</u> <u>3157</u>	-20850 <u>917</u>	
16	.eflunomide-Model_5 .eflunomide-Model_5	Phase	-1004	18464	-0.054	0.957	37104	-39112	
	.etIunomide-Model_5	Interact	-931	. 985	-0.945	0.356	1102	-2965	
47-									
	ARIMA(0,0,0) Natural Logarithm, No		Parameter						
49	Transformation Sulfasalazine-Model_1	(Step); Interact (After) Sulfasalazine	Estimate 16.041					CI 15.987339	
50	Sulfasalazine-Model_1 Sulfasalazine-Model_1	TimePeriod	0.001	0.003	0.179	0.86	0.007	-0.005	
50	ulfasalazine-Model_1	Phase	0.067		0.707	0.488	0.261	-0.127	
51	ulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2	Interact Hydroxychloroquinesulfate	-0.004 15.368		-0.715 597.458	0.483 0	0.006	-0.014 15.314	
52	hydroxychloroquinesulfate-Model_2	TimePeriod	-0.002	0.003	-0.778	0.445	0.004	-0.008	
52	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase	0.163		1.776	0.09	0.353	-0.027	
	Azathioprine-Model_3	Interact Azathioprine	-0.005 15.336		-0.887 653.382	0.385 0	0.005 15.383	-0.015 15.289	
54,	Azathioprine-Model_3 Azathioprine-Model_3	TimePeriod	-0.003	0.003	-0.986	0.335	0.003	-0.009	
55	Azathioprine-Model_3	Phase	0.171		2.046	0.053	0.344	-0.002	
56	Azathioprine-Model_3 Methotrexate-Model_4	Interact Methotrexate	-0.007 15.22		-1.404 631.677	0.175 0	0.003	-0.017 15.170	
¹	Vethotrexate-Model_4 Vethotrexate-Model_4	TimePeriod	0.002	0.003	0.687	0.499	0.008	-0.004	
5/	Methotrexate-Model_4	Phase	0.059		0.687	0.5	0.236	-0.118	
58	Methotrexate-Model_4 Methotrexate-Model_4 .eflunomide-Model_5	Interact Leflunomide	-0.003 13.2		-0.512 512.174	0.614 0	0.007 13.254	-0.013 13.146	
59	eflunomide-Model_5	TimePeriod	0.001	0.003	0.348	0.731	0.007	-0.005	
	eflunomide-Model_5	Phase	0.054		0.584	0.565	0.244	-0.136	
00	.eflunomide-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 (23^d Mar-20) until 11 months after this date (Mar-20 to Jan-21).

-0.00319 -0.26371 -0.01338 -0.00419 -0.1718 -0.01638 -0.00619 -0.06471 -0.02038 -0.00219 -0.22339 -0.01132 -0.00319

-0.24877 -0.01232

-0.00113 -0.17954 -0.00926 -0.00213 -0.10201 -0.01432

-0.00413 -0.02862 -0.01832 0.001936 -0.14077 -0.00619 -0.00013 -0.17435 -0.00826

-0.00632 -0.51557 -0.01664 -0.00432 -0.47133 -0.02164 -0.00732 -0.36473 -0.02058 -0.02058 -0.02164 -0.02632 -0.43376 -0.02064

0.000936 -0.11045 -0.00919 -0.00106 -0.00822 -0.01219 -0.02156 -0.00219 0.0051613 -0.01519 0.001936 -0.08717 -0.00513 0.001936 -0.11843 -0.01413

10591.88 -966611 -79427.8 -5282.23 25787.17 -630388 -8569.8 230048.1 -63875 10455.29 -370894 -16072.2 1149.135 -64142.3 -64142.3

1 2	ARIMA Model Parameters	ARIMA (March	20+ is a '0')					
3	ARIMA(0,0,0), No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
4	Sulfasalazine-Model_1	TimePeriod	0.003		1.091		0.009192	
5	Sulfasalazine-Model_1 Sulfasalazine-Model 1	Phase Interact	-0.047 -0.001		-0.449 -0.091	0.658 0.929		
	Hydroxychloroquinesulfate-Model_2	TimePeriod	0.002		0.565		0.008192	
6	Hydroxychloroquinesulfate-Model_2	Phase	0.08		0.655		0.331796	
7	Hydroxychloroquinesulfate-Model_2	Interact	-0.004		-0.618		0.008383	
8	Azathioprine-Model_3 Azathioprine-Model 3	TimePeriod Phase	0 0.152		-0.167 1.451		0.006192 0.368709	
9	Azathioprine-Model_3	Interact	-0.008		-1.362		0.004383	
10	Methotrexate-Model_4	TimePeriod	0.004		1.552	0.136	0.010192	-0.00
11	Methotrexate-Model_4	Phase	-0.017		-0.171	0.866	0.18939	
	Methotrexate-Model_4 Leflunomide-Model 5	Interact TimePeriod	-0.001 0.003		-0.113 1.193		0.009319 0.009192	
12	Leflunomide-Model_5	Phase	-0.03		-0.285	0.778		
13	Leflunomide-Model_5	Interact	0.00006631	0.006	0.012	0.991	0.01245	-0.0
14								
15	ARIMA(1,0,0), AR		Estimate	Standard Error	t	P-value	UCI	LCI
16	Sulfasalazine-Model_1	TimePeriod	0.003		1.716		0.007128	
17	Sulfasalazine-Model_1	Phase	-0.033	0.071	-0.459	0.651	0.113537	-0.1
	Sulfasalazine-Model_1	Interact	-0.001		-0.328		0.007256	
18	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	0.002		0.722 0.983		0.006128	
19	Hydroxychloroquinesulfate-Model 2	Interact	-0.004		-0.907		0.006319	
20	Azathioprine-Model_3	TimePeriod	0		-0.143	0.888		
21	Azathioprine-Model_3	Phase	0.153		1.744		0.334623	
	Azathioprine-Model_3	Interact	-0.008		-1.677		0.002319	
22	Methotrexate-Model_4 Methotrexate-Model_4	TimePeriod Phase	0.004		2.719 -0.323	0.013	0.006064 0.10277	
23	Methotrexate-Model 4	Interact	0.015		-0.117		0.006192	
24	Leflunomide-Model_5	TimePeriod	0.004	0.002	2.073	0.051	0.008128	-0.0
25	Leflunomide-Model_5	Phase	-0.034		-0.498		0.106345	
26	Leflunomide-Model_5	Interact	0	0.004	0.056	0.956	0.008256	-0.00
27	ARIMA(0,1,0), Difference		Estimate	Standard Error	t	P-value	UCI	LCI
28	Sulfasalazine-Model_1	TimePeriod	0.004		0.721		0.014319	
29	Sulfasalazine-Model_1	Phase Interact	-0.142 0.004		-0.786 0.417		0.231566 0.024639	
30	Sulfasalazine-Model_1 Hydroxychloroquinesulfate-Model_2	TimePeriod	0.004		1.089		0.024039	
31	Hydroxychloroquinesulfate-Model_2	Phase	-0.073		-0.38		0.325332	
32	Hydroxychloroquinesulfate-Model_2	Interact	-0.001		-0.084		0.019639	
	Azathioprine-Model_3	TimePeriod	0.003		0.741		0.013319	
33	Azathioprine-Model_3 Azathioprine-Model 3	Phase Interact	-0.018 -0.002		-0.109		0.328735 0.016575	
34	Methotrexate-Model_4	TimePeriod	0.003		0.638		0.013319	
35	Methotrexate-Model_4	Phase	-0.041	0.178	-0.228		0.326374	
36	Methotrexate-Model_4	Interact	-0.001		-0.06		0.019639	
37	Leflunomide-Model_5 Leflunomide-Model 5	TimePeriod Phase	0.004 -0.054		0.731 -0.291		0.014319	
	Leflunomide-Model_5	Interact	0		-0.025		0.020639	
38								
39			Estimate	Chandrad France		Duralua		
40	ARIMA(0,0,1), MA, Natural Log Sulfasalazine-Model 1	TimePeriod	Estimate 0.003	Standard Error 0.001	τ 3.399	P-value	0.005064	LCI
41	Sulfasalazine-Model_1	Phase	0.001		0.015		0.112451	
42	Sulfasalazine-Model_1	Interact	-0.003	0.003	-1.114	0.278	0.003192	-0.00
	Hydroxychloroquinesulfate-Model_2	TimePeriod	0.001		0.987		0.003064	
43	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	0.128 -0.006		1.949 -1.952		0.264217 0.000192	
44	Azathioprine-Model_3	TimePeriod	-0.00002175		-0.023		0.002042	
45	Azathioprine-Model_3	Phase	0.161		3.059		0.270387	
46	Azathioprine-Model_3	Interact	-0.009		-3.398	<u>0.003</u>		
47	Methotrexate-Model_4	TimePeriod Phase	0.004 -0.017		5.374 -0.509		0.006064	
	Methotrexate-Model_4 Methotrexate-Model_4	Interact	-0.017		-0.309		0.003173	
48	Leflunomide-Model_5	TimePeriod	0.004		4.722			
49	Leflunomide-Model_5	Phase	-0.04		-1.044	0.309		
50	Leflunomide-Model_5	Interact	0	0.002	0.058	0.954	0.004128	-0.00
51	ARIMA(0,0,1), MA, No Transformation		Estimate	Standard Error	t	P-value	UCI	LCI
52	Sulfasalazine-Model_1	TimePeriod	26528.53		3.436		42465.18	
	Sulfasalazine-Model_1	Phase	44198.442		0.09	0.929		
53	Sulfasalazine-Model_1	Interact	-29893.865				19640.07	
54	Hydroxychloroquinesulfate-Model_2	TimePeriod Phase	5769.508		1.077		16821.25	
55	Hydroxychloroquinesulfate-Model_2 Hydroxychloroquinesulfate-Model_2	Phase Interact	687248.921 -32332.165			<u>0.044</u> <u>0.042</u>		
56	Azathioprine-Model_3	TimePeriod	-32332.103 83.53		0.02		8736.858	
57	Azathioprine-Model_3	Phase	733233.954	243803.562	3.007	<u>0.007</u>	1236420	2300
	Azathioprine-Model_3	Interact	-39498.697			0.003		
58	Methotrexate-Model_4	TimePeriod Phase	16630.548					
59	Methotrexate-Model_4 Methotrexate-Model_4	Phase Interact	-80776.956 -2192.432				209340.4 11687.38	
60	Leflunomide-Model_5	TimePeriod	2041.806		4.721	<u>0.0001</u>		
	Leflunomide-Model_5	Phase	-21148.135	20831.545	-1.015		21846.06	-641
	Leflunomide-Model_5	Interact	28.158	1010.937	0.028	0.978	2114.629	-205

```
Page 27 of 44 #Changepoint Analysis
                                              BMJ Open
     2
         #install.packages("changepoint")
     3
         library(changepoint)
1
     4
         #install.packages("changepoint.np")
2
        library(changepoint.np)
     5
3
         #install.packages("EnvCpt")
     6
4
     7
         library(EnvCpt)
5
     8
         library(ggplot2)
         library(lubridate)
6
     9
7
    10
         install.packages("rmarkdown")
    11
8
    12
9
   13
         data <- read.delim("C:\\Users\\rb1097\\OneDrive - University of Brighton\\Chp 8, 10</pre>
10
         RA Folder\\BMJ Open\\R3\\Data.csv", sep = ",")
11
   14
         data$Sulfasalazine<-as.numeric(data$Sulfasalazine)</pre>
12
         data$Hydroxychloroquine.sulfate<-as.numeric(data$Hydroxychloroquine.sulfate)</pre>
    15
13
         data$Azathioprine<-as.numeric(data$Azathioprine)</pre>
    16
14
    17
         data$Methotrexate<-as.numeric(data$Methotrexate)</pre>
15
         data$Leflunomide<-as.numeric(data$Leflunomide)</pre>
    18
16
    19
        class(Sulfasalazine)
17
    20
        class(data$i..Month) # "character"
18
    21
19
    22 data$i..Month<-as.POSIXct(strptime("01/01/2019", "%d-%m-%Y"))</pre>
20
    23
       class(data$i..Month) # "POSIXct" "POSIXt"
21
    24
22
   25 data$ï..Month
23
   2.6
       #data
24
   27
        #class(object)
25
   28
26
   29
       head(data)
27
   30
         View(data)
   31
28
        length(data)
29
   32
         summary(data)
    33
30
         ts.plot(data,xlab="Time in months",ylab="Prescription Quantity")
    34
31
    35
32
    36
         _____
33
    37
         data.amoc=cpt.mean(data$Sulfasalazine)
34
    38
         means=param.est(data.amoc)$mean
35
    39
         data$Sulfasalazine.resid=data$Sulfasalazine-rep(means, seq.len(data.amoc))
36
   40
         shapiro.test(data$Sulfasalazine.resid)
37
   41
        #Shapiro-Wilk normality test
38
    42
         #data: data$Sulfasalazine.resid
39
    43
         \#W = 0.97663, p-value = 0.8113
40
    44
41
    45
42
    46
         ks.test(data$Sulfasalazine.resid, pnorm, mean=mean(data$Sulfasalazine.resid), sd=sd(data$
43
         Sulfasalazine.resid))
44
   47
         #One-sample Kolmogorov-Smirnov test
45
   48
         #data: data$Sulfasalazine.resid
46
   49
         \#D = 0.10639, p-value = 0.9114
47
   50
         #alternative hypothesis: two-sided
48
   51
         ### Below, we have tried varied methods: Choice of "AMOC", "PELT", "SegNeigh" or
49
   52
         "BinSeg"
50
    53
51
         Mean_Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC", pen.value = 0, method</pre>
   54
52
         = "AMOC", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
53
    55
         Mean Variance # Calculates the optimal positioning and (potentially) number of
54
         changepoints for data
55
    56
56
         #Created Using changepoint version 2.2.3
    57
57
    58
         #Changepoint type : Change in mean and variance
58
    59
         #Method of analysis
                                : AMOC
59
    60
         #Test Statistic : Normal
60
    61
         #Type of penalty : MBIC with value, 9.656627 (Minimum Bayesian information
         criterion)
    62
         #Minimum Segment Length : 2
         #Maximum no. of cpts
    6.3
                                • 1
         #Changepoint For per review only - http://hmiopen.hmj.com/site/about/guidelinesettmlsing this method)
    64
    65
```

```
BMJ Open
                                                                                          Page 28 of 44
    66
         Mean Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC", pen.value = 0, method
    67
         = "PELT", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
1
    68
         Mean Variance # Calculates the optimal positioning and (potentially) number of
2
         changepoints for data
3
         #Created Using changepoint version 2.2.3
    69
4
    70
                               : Change in mean and variance
         #Changepoint type
5
    71
         #Method of analysis
                                : PELT
    72
6
         #Test Statistic : Normal
    73
7
         #Type of penalty
                                : MBIC with value, 12.8755 (Minimum Bayesian information
         criterion)
8
    74
         #Minimum Segment Length : 2
9
    75
         #Maximum no. of cpts : Inf
10
    76
         #Changepoint Locations : (No Changepoint detected using this method)
11
    77
12
    78
13
         Mean Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC", pen.value = 0, method
    79
14
         = "SegNeigh", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=
15
         2)
16
    80
         Mean Variance # Calculates the optimal positioning and (potentially) number of
17
         changepoints for data
18
    81
         #Created Using changepoint version 2.2.3
19
         #Changepoint type : Change in mean and variance
#Method of analysis : AMOC
    82
20
    83
21
    84
         #Test Statistic : Normal
22
    8.5
         #Type of penalty
                                : MBIC with value, 9.656627
23
    86
         #Minimum Segment Length : 2
24
    87
         #Maximum no. of cpts : 1
25
    88
         #Changepoint Locations : 24 (Changepoint at Dec 2020 detected using this method)
26
    89
         Mean Variance <-cpt.meanvar(data$Sulfasalazine, penalty = "MBIC", pen.value = 0, method
27
    90
         = "BinSeg",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2)
28
         Mean Variance # Calculates the optimal positioning and (potentially) number of
29
    91
         changepoints for data
30
    92
31
    93
         #Created Using changepoint version 2.2.3
32
         #Changepoint type : Change in mean and variance
#Method of analysis : BinSeg
    94
33
    95
34
    96
         #Test Statistic : Normal
35
    97
         #Type of penalty : MBIC with value, 12.8755
36
    98
         #Minimum Segment Length : 2
37
    99
         #Maximum no. of cpts : 5
38 100
         #Changepoint Locations :
39 101
         # Range of segmentations:
40 102
         # [,1] [,2] [,3] [,4] [,5]
41 103
         #[1,] 16 NA NA NA
                                      NA
42 104
         #[2,] 16 14
                          NA NA
                                     NA
                                            Change points relate to: 16 (April 2020), 14 (Feb
43
         2020),22 (Oct 2020), 20 (Aug 2020), 12 (Dec 19)
44 105
         #[3,] 16 14 22 NA
                                    NA
45 106
                           22
         #[4,]
                 16 14
                                20
                                      NA
46 107
         #[5,]
                 16
                    14
                          22
                               20
                                    12
47 108
48 109
         #For penalty values: 0.7861357 0.7861357 0.7861357 0.7861357 0.7861357
49 110
         -----
50 111
         data.amoc=cpt.mean(data$Hydroxychloroquine.sulfate)
51 112
         means=param.est(data.amoc)$mean
52 113
         data$Hydroxychloroquine.sulfate.resid=data$Hydroxychloroquine.sulfate-rep(means,
         seg.len(data.amoc))
53
54 <sup>114</sup>
         shapiro.test(data$Hydroxychloroquine.sulfate.resid)
55 <sup>115</sup>
         #Shapiro-Wilk normality test
56 <sup>116</sup>
         #data: data$Hydroxychloroquine.sulfate.resid
57 <sup>117</sup>
         \#W = 0.98426, p-value = 0.9545
   118
58
   119
59
   120
         ks.test(data$Hydroxychloroquine.sulfate.resid,pnorm,mean=mean(data$
60
         Hydroxychloroquine.sulfate.resid), sd=sd (data$Hydroxychloroquine.sulfate.resid))
   121
         #One-sample Kolmogorov-Smirnov test
   122
         #data: data$Hydroxychloroquine.sulfate.resid
   123
         \#D = 0.12088, p-value = 0.8164
         #alternative Rypeenreview.onlyohttp://bmjopen.bmj.com/site/about/guidelines.xhtml
   124
   125
```

```
Page 29 of 44
```

BMJ Open

```
127
   128
         Mean Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC",
1
         pen.value = 0, method = "AMOC", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE,
2
         shape=1,minseglen=2)
3
  129
         Mean Variance # Calculates the optimal positioning and (potentially) number of
4
         changepoints for data
  130
5
          #Created Using changepoint version 2.2.3
  131
6
         #Changepoint type
                               : Change in mean and variance
7
  132
         #Method of analysis
                                  : AMOC
  133
         #Test Statistic : Normal
8
   134
         #Type of penalty
                                  : MBIC with value, 9.656627
9
10 135
         #Minimum Segment Length : 2
11 136
         #Maximum no. of cpts
                                 : 1
12 <sup>137</sup>
         #Changepoint Locations : 24
13 <sup>138</sup>
   139
         Mean Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC",
14
         pen.value = 0, method = "PELT", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE,
15
         shape=1,minseglen=2)
16
  140
         Mean Variance # Calculates the optimal positioning and (potentially) number of
17
         changepoints for data
18 141
              Created Using changepoint version 2.2.3
         #
19
  142
         #
              Changepoint type
                                    : Change in mean and variance
20 143
         #
             Method of analysis : PELT
21 144
         #
             Test Statistic : Normal
22 145
         #
             Type of penalty
                                    : MBIC with value, 12.8755
23 146
         #
            Minimum Segment Length : 2
24 147
         #
            Maximum no. of cpts
                                    : Inf
25 148
         # Changepoint Locations :
26 149
27 150
28 151
         Mean_Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC",</pre>
29
         pen.value = 0,method = "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=
         TRUE, shape=1, minseglen=2)
30
31 152
         Mean Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
32
33 <sup>153</sup>
              Created Using changepoint version 2.2.3
         #
34 <sup>154</sup>
                                   : Change in mean and variance
: PELT
         #
              Changepoint type
35 <sup>155</sup>
         #
             Method of analysis
36 <sup>156</sup>
         #
             Test Statistic : Normal
  157
                                  : MBIC with value, 12.8755
         #
             Type of penalty
37
37 158 38 159
         #
             Minimum Segment Length : 2
         #
             Maximum no. of cpts
                                    : Inf
39 <sup>-</sup> 160
         #
             Changepoint Locations :
40 <sup>.</sup> 161
41 162
42 163
         Mean Variance <-cpt.meanvar(data$Hydroxychloroquine.sulfate, penalty = "MBIC",
43
         pen.value = 0, method = "BinSeg", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE
44
         , shape=1, minseglen=2)
45 164
         Mean Variance # Calculates the optimal positioning and (potentially) number of
46
         changepoints for data
47 165
48 166
         #
              Created Using changepoint version 2.2.3
49 167
              Changepoint type : Change in mean and variance
         #
50 168
              Method of analysis
                                     : BinSeg
         #
51 169
              Test Statistic : Normal
         #
52 170
                                      : MBIC with value, 12.8755
         #
              Type of penalty
53 <sup>171</sup>
              Minimum Segment Length : 2
         #
54 <sup>172</sup>
         #
             Maximum no. of cpts
                                     : 5
55 <sup>173</sup>
         #
              Changepoint Locations :
56 <sup>174</sup>
         #
              Range of segmentations:
57 <sup>175</sup>
         #
                   [,1] [,2] [,3] [,4] [,5]
                   14
   176
         #
              [1,]
                         NA
                               NA
                                    NA
                                         NA
58
   177
         #
              [2,]
                     14
                          17
                               NA
                                     NA
                                          NA # changepoint 14 is Feb-20, changepoint
                                                                                         17
59
         May-20, changepoint 12 Dec-19, changepoint 10 Oct-19, changepoint 20 Aug-20
60
  178
                         17
         #
              [3,] 14
                               12
                                    NA
                                         NA
   179
         #
              [4,]
                          17
                                12
                     14
                                     10
                                           NA
         #
   180
              [5,]
                          17
                                12
                                     10
                                           20
                     14
         #
   181
               For penafier, peer review only 7 http://brgiopen.brgi.com/site/about/guidelines.khmb258
   182
          #
   183
```

```
_____<u>BM</u>J Open
                                                                                             Page 30 of 44
   184
   185
   186
         data.amoc=cpt.mean(data$Azathioprine)
1
  187
         means=param.est(data.amoc)$mean
2
  188
         data$Azathioprine.resid=data$Azathioprine-rep(means, seg.len(data.amoc))
3
  189
         shapiro.test(data$Azathioprine.resid)
4
  190
         #Shapiro-Wilk normality test
  191
5
         #data: data$Azathioprine.resid
  192
6
         \#W = 0.96776, p-value = 0.5889
7
   193
  194
8
   195
         ks.test(data$Azathioprine.resid, pnorm, mean=mean(data$Azathioprine.resid), sd=sd(data$
9
         Azathioprine.resid))
10
11 196
         #One-sample Kolmogorov-Smirnov test
12 <sup>197</sup>
         #data: data$Azathioprine.resid
         \#D = 0.1164, p-value = 0.8489
   198
13
   199
         #alternative hypothesis: two-sided
14
   200
15
   201
         Mean Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC", pen.value = 0, method =
16
          "AMOC", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
17
   202
         Mean Variance # Calculates the optimal positioning and (potentially) number of
18
         changepoints for data
19
   203
             Created Using changepoint version 2.2.3
         #
20 204
         #
             Changepoint type
                                     : Change in mean and variance
21 205
         #
             Method of analysis
                                    : AMOC
22 206
         #
             Test Statistic : Normal
23 207
         #
             Type of penalty
                                    : MBIC with value, 9.656627
24 208
         #
             Minimum Segment Length : 2
25 209
         #
             Maximum no. of cpts
                                   : 1
26 210
             Changepoint Locations : 24
         #
27 211
28 212
29 213
         Mean Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC",pen.value = 0,method =
          "PELT", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
30
31 214
         Mean Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
32
33 215
         #
             Created Using changepoint version 2.2.3
34 <sup>216</sup>
                                   : Change in mean and variance
             Changepoint type
         #
35 <sup>217</sup>
         #
             Method of analysis
                                    : PELT
36<sup>218</sup>
         #
             Test Statistic : Normal
         #
   219
             Type of penalty
                                 : MBIC with value, 12.8755
37
   220
         #
             Minimum Segment Length : 2
38
   221
         #
             Maximum no. of cpts
                                   : Inf
39 222
         #
             Changepoint Locations :
40 <sub>223</sub>
41 224
42 225
         Mean Variance <-cpt.meanvar(data$Azathioprine, penalty = "MBIC", pen.value = 0, method =
43
          "SegNeigh", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2
44
         )
45 226
         Mean Variance # Calculates the optimal positioning and (potentially) number of
46
         changepoints for data
47 227
         # SegNeigh is computationally slow, use PELT instead
48 228
49 229
         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)
50
51 230
         Mean_Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
52
53 <sup>231</sup>
             Created Using changepoint version 2.2.3
         #
54 <sup>232</sup>
             Changepoint type
         #
                                     : Change in mean and variance
55 <sup>233</sup>
         #
             Method of analysis
                                     : BinSeg
56 <sup>234</sup>
         #
             Test Statistic : Normal
                                    : MBIC with value, 12.8755
   235
         #
             Type of penalty
57
   236
         #
             Minimum Segment Length : 2
58
   237
         #
             Maximum no. of cpts
                                   : 5
59
   238
         #
             Changepoint Locations :
60
   239
         #
             Range of segmentations:
   240
         #
                  [,1] [,2] [,3] [,4] [,5]
   241
         #
              [1,]
                    19
                          NA
                              NA
                                    NA
                                          NA
                               NA
                                     NA
                                          NA #Changepoint 19 (July 20), Changepoint 16 (April
   2.42
         #
              [2,]
                    19
                          16
         20), ChangepoForpergreviewozly-http://bmjepen.hmj.com/bie/abgyt/gwidelinespbime 10 (Oct 19)
                                          NA
   243
             [3,]
                   19
                          16
                                14
                                   NA
         #
```

```
BMJ Open
Page 3_1 1_4 of 44_{\#}
                     19
              [4, ]
                           16
                                14
                                      12
                                           NA
   245
          #
              [5,]
                    19
                           16
                                14
                                      12
                                           10
   246
          #
1
               For penalty values: 2.656231 2.656231 2.656231 2.656231 2.656231
   247
          #
2
  248
3
  249
          _____
4
  250
         data.amoc=cpt.mean(data$Methotrexate)
  251
5
         means=param.est(data.amoc)$mean
         data$Methotrexate.resid=data$Methotrexate-rep(means,seg.len(data.amoc))
6
  252
   253
7
         shapiro.test(data$Methotrexate.resid)
  254
          #Shapiro-Wilk normality test
8
   255
          #data: data$Methotrexate.resid
9
10 256
          \#W = 0.99406, p-value = 0.9999
11 <sup>257</sup>
12 <sup>258</sup>
  259
         ks.test(data$Methotrexate.resid, pnorm, mean=mean(data$Methotrexate.resid), sd=sd(data$
13
         Methotrexate.resid))
15 260
         # One-sample Kolmogorov-Smirnov test
16 <sup>2</sup><sub>262</sub>
   261
         #data: data$Methotrexate.resid
         \#D = 0.070042, p-value = 0.9989
17
   263
         #alternative hypothesis: two-sided
18 <sup>2</sup>64
19
   265
20 266
         Mean Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC", pen.value = 0, method =
21
          "AMOC", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseqlen=2)
22 267
         Mean Variance # Calculates the optimal positioning and (potentially) number of
23
         changepoints for data
24 268
              Created Using changepoint version 2.2.3
         #
25 269
             Changepoint type
                                    : Change in mean and variance
         #
26 270
             Method of analysis
                                    : AMOC
         #
27 271
             Test Statistic : Normal
         #
28 272
         #
              Type of penalty
                                 : MBIC with value, 9.656627
29 273
         #
             Minimum Segment Length : 2
30 274
         #
             Maximum no. of cpts : 1
31 275
          #
             Changepoint Locations : 24
32 276
33 <sup>277</sup>
         Mean Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC", pen.value = 0, method =
          "PELT", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
34
  278
         Mean Variance # Calculates the optimal positioning and (potentially) number of
35
         changepoints for data
36
   279
             Created Using changepoint version 2.2.3
         #
37
37
38 280
281
             Changepoint type : Change in mean and variance
Method of analysis : PELT
         #
         #
39 <sup>-</sup> <sub>282</sub>
         #
             Test Statistic : Normal
40 <sup>–</sup> <sub>283</sub>
          #
             Type of penalty
                                  : MBIC with value, 12.8755
41 <sup>-</sup> <sub>284</sub>
         #
             Minimum Segment Length : 2
42 285
         # Maximum no. of cpts
                                    : Inf
43 286
          # Changepoint Locations :
44 287
45 288
46 289
         Mean Variance <-cpt.meanvar(data$Methotrexate, penalty = "MBIC", pen.value = 0, method =
47
           "SegNeigh",Q=5,test.stat="Normal",class=TRUE,param.estimates=TRUE,shape=1,minseglen=2
48
         )
49 290
         Mean Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
50
51 291
          #SegNeigh is computationally slow, use PELT instead (returns PELT method results)
52 292
53 <sup>293</sup>
54 <sup>294</sup>
         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)
55
  295
         Mean Variance # Calculates the optimal positioning and (potentially) number of
56
         changepoints for data
57
   296
             Created Using changepoint version 2.2.3
          #
58
   297
          #
              Changepoint type : Change in mean and variance
59
   298
         #
             Method of analysis
                                    : BinSeg
60 299
         #
             Test Statistic : Normal
   300
         #
             Type of penalty
                                    : MBIC with value, 12.8755
   301
         #
             Minimum Segment Length : 2
   302
         #
             Maximum no. of cpts
              Changepoiner per review gnly - http://bmjopen.bmj.com/site/about/guidelines.xhtml
         #
   303
   304
          #
              Range of segmentations:
```

```
Page 32 of 44
                                               BMJ Open
                   [,1] [,2] [,3] [,4] [,5]
   305
         #
   306
         #
              [1,]
                     4 NA NA
                                   NA NA
             [2,]
   307
                      4
                          20
                              NA
                                   NA
                                         NA #Changepoint 4 is Apr-19, Changepoint 20
         #
1
         Oct-19, Changepoint 13 Jan-20, Changepoint 4 Apr-19, Changepoint 11 Nov-19,
2
         Changepoint 16 Apr-20
3
  308
                          20
             [3,]
                     4
                               13
                                     NA
                                          NA
         #
4
  309
                      4
                          20
                               13
         #
              [4,]
                                     11
                                          NA
  310
5
         #
              [5,]
                      4
                          20
                                13
                                     11
                                          16
  311
6
         #
7
   312
         #
               For penalty values: 2.821485 0.472209 0.4089625 0.4089625 0.4089625
  313
8
   314
9
10 315
         _____
11 316
         data.amoc=cpt.mean(data$Leflunomide)
12 <sup>317</sup>
         means=param.est(data.amoc)$mean
  318
         data$Leflunomide.resid=data$Leflunomide-rep(means, seg.len(data.amoc))
13
   319
         shapiro.test(data$Leflunomide.resid)
14
   320
         #Shapiro-Wilk normality test
15
         #data: data$Leflunomide.resid
   321
16 <sub>322</sub>
         \#W = 0.79083, p-value = 0.0001605
17
   323
18 324
19
   325
         ks.test(data$Leflunomide.resid, pnorm, mean=mean(data$Leflunomide.resid), sd=sd(data$
20
         Leflunomide.resid))
21 326
         #One-sample Kolmogorov-Smirnov test
22 327
         #data: data$Leflunomide.resid
23 328
         \#D = 0.26919, p-value = 0.04329
24 329
         #alternative hypothesis: two-sided
25 330
26 331
27 332
         Mean_Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC", pen.value = 0, method =</pre>
         "AMOC", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
28
29 333
         Mean Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
30
31 334
         #
             Created Using changepoint version 2.2.3
32 <sup>335</sup>
                                : Change in mean and variance
s : AMOC
         #
             Changepoint type
33 <sup>336</sup>
         #
             Method of analysis
34 <sup>337</sup>
         #
             Test Statistic : Normal
35 <sup>338</sup>
         #
             Type of penalty
                                 : MBIC with value, 9.656627
36 <sup>339</sup>
             Minimum Segment Length : 2
         #
             Maximum no. of cpts : 1
   340
         #
37
38 342
   341
         #
             Changepoint Locations : 24
39 343
40 344
         Mean Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC",pen.value = 0,method =
41
         "PELT", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
42 345
         Mean Variance # Calculates the optimal positioning and (potentially) number of
43
         changepoints for data
44 346
             Created Using changepoint version 2.2.3
         #
45 347
         #
             Changepoint type : Change in mean and variance
46 348
             Method of analysis
                                    : PELT
         #
47 349
             Test Statistic : Normal
         #
48 350
             Type of penalty
                                    : MBIC with value, 12.8755
         #
49 351
             Minimum Segment Length : 2
         #
50 352
             Maximum no. of cpts
         #
                                   : Inf
51 353
             Changepoint Locations :
         #
52 <sup>354</sup>
53 <sup>355</sup>
54 <sup>356</sup>
         Mean Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC", pen.value = 0, method =
         "SeqNeigh", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseqlen=2)
55
  357
         Mean Variance # Calculates the optimal positioning and (potentially) number of
56
         changepoints for data
57
   358
         #
             SegNeigh is computationally slow, use PELT instead (returns PELT method results)
58
   359
59
   360
         Mean Variance <-cpt.meanvar(data$Leflunomide, penalty = "MBIC", pen.value = 0, method =
60
         "BinSeg", Q=5, test.stat="Normal", class=TRUE, param.estimates=TRUE, shape=1, minseglen=2)
   361
         Mean Variance # Calculates the optimal positioning and (potentially) number of
         changepoints for data
   362
             Created Using changepoint version 2.2.3
         #
              Changepoiner per eview only - http://bmjopen.emj.com/site/about/guidelines.xhtml
   363
         #
   364
         #
             Method of analysis
                                    : BinSeg
```

Page 33 of 44	Test Statistic · Normal BMJ Open
000 1	Test Statistic : Normal BMJ Open Type of penalty : MBIC with value, 12.8755
367 #	Minimum Segment Length : 2
1 368 # 2 369 #	Maximum no. of cpts : 5 Changepoint Locations :
3 370 #	
	[,1] [,2] [,3] [,4] [,5]
5 372 # 6 373 #	<pre>[1,] 7 NA NA NA NA [2,] 7 5 NA NA NA Changepoint 7 is Jul-19, Changepoint 5 is May-19,</pre>
7 Cha	angepoint 3 is Mar-19, Changepoint 20 is Aug-20, Changepoint 16 is Apr-20
8 374 # 9 375 #	[3,] 7 5 3 NA NA [4,] 7 5 3 20 NA
10 376 #	[4,] 7 5 3 20 NA [5,] 7 5 3 20 16
11 ³⁷⁷ # 12 ³⁷⁸ #	For penalty values: 1.181572 1.181572 0.8537313 0.2305199 0.2305199
13	
14	
15 16	
17	
18 19	
20	
21 22	
23	
24 25	
26	
27 28	
29	
30 31	
32	
33 34	
35 36	
37	
38 39	
40	
41 42	
43	
44 45	
46	
47 48	
49	
50 51	
52	
53	
54 55 56	
56 57	
57 58	
59 60	
ου	

BMJ Open Supplementary Table 3 - Quantity & Cost														Page 34 of 44											
1 Supplementary	Tabl	le 3 -	- 0ua	antit	v & (^ost												1-202							
1	100		Quu	litte	yuu	2030												21-0							
2 3																		519							
4																		36 (
5																		on 2							
6 Supplemental Results (Total Quantity)																		<u>3</u>							
7 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-26000000000000000000000000000000000000	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21 Trend
8 Sulfasalazine Hydroxychloroquine sulfate	9.54 4.89	8.61 4.37	9.33 4.69	9.15 4.57	9.68 4.93	9.07 4.51	9.26 4.67	9.88 4.88	9.12 4.52	9.65 4.79	9.23 4.56	9.32 4.69	9.79 4.66	8.64 4.29	10.26 5.37	9.45 5.11	8.94 4.70	9.000 4.700	9.43 4.91	8.51 4.41	9.18 4.78	9.07 4.84	8.89 4.66	9.75 5.02	9.38
9 Azathioprine Methotrexate	4.69 4.19	4.24 3.81	4.54 4.12	4.45 4.05	4.74 4.32	4.38 3.98	4.45 4.11	4.72 4.39	4.43 4.05	4.65 4.31	4.46 4.13	4.52 4.26	4.45 4.27	4.11 3.90	4.81 4.54	4.90 4.26	4.52 4.08	4.5 4.22	4.54 4.40	4.09 3.98	4.42 4.29	4.44 4.33	4.27 4.18	4.62 4.55	4.30 ······ 4.17 ·····
1 Q ^{Methotrexate} 1 J ^T able 1 Total Quantity; Monthly Subtotal (in millio	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	^{4.2} 2022.	0.56	0.52	0.56	0.57	0.55	0.59	0.55
12	1157																								
1 Supplemental Results (Actual Cost)	40						140	- 10 - 0			·	10 10	20 5	1.00 M			22 II			- 22					
4 ulfasalazine	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	un-20 Sju 0.60 0.40	0.70	0.64	0.69	0.69	0.73	0.82	0.81 ~~~~
Hydroxychloroquine sulfate	0.30 0.19	0.27 0.17	0.29 0.18	0.28	0.39 0.21	0.49 0.19	0.45 0.20	0.45	0.38 0.21	0.37 0.22	0.35 0.21	0.36	0.54 0.32	0.50 0.20	0.62	0.77 0.59	0.55 0.47	0.4 0.4 4.4 6 4.4	0.51 0.27	0.46 0.24	0.50 0.26	0.54 0.24	0.53 0.23	0.56	0.57
16 ^{Aethotrexate} Leflunomide	3.27 0.12	3.12 0.10	3.45 0.11	3.43 0.11	3.73 0.12	3.52 0.11	3.75 0.11	4.01	3.85 0.12	4.15 0.12	4.02	4.21 0.12	4.29 0.12	3.96 0.11	4.70 0.12	4.47 0.10	4.26	4.4	4.67 0.10	4.33 0.10	4.65 0.10	4.68 0.10	4.56 0.09	4.94 0.10	4.63
17Table 2 Actual Cost; Monthly Subtotal (in £million																		ded from http://bmjopen.bmj.com/ on April 23, 2024							
18																		htt							
19 20																		p://t							
21																		- mj							
22																		ope							
23																		http://bmjopen.bmj.com/ on April 23, 2024 by g							
24																		<u>, n</u>							
25																		ğ							
26 27																		or							
28																		Ap							
29																		Ť.							
30																		ω̈́							
31																		202							
32																		4 by							
33																		ng							
34 35																		est.							
36																		Pro							
37																		otec							
38																		ted							
39																		by							
40																		uest. Protected by copyright.							
41																		oyri							
42																		ght.							
43 44						For pe	er revi	iew on	ly - htt	:p://bn	njopen	.bmj.co	om/sit	e/abou	ut/guio	delines	s.xhtml								
45																									
46																									

mjopen-2021-051936 on 23 Supplementary Table 4 - Region 1 2 3 4 5 6 Aug-19 Sec.20 Total Quantity by region Jan-19 Feb-19 Mar-19 Apr-19 Mav-19 Jun-19 Jul-19 Sep-19 Oct-19 Nov-19 Dec-19 Jan-20 Feb-20 Mar-20 Apr-20 Mav-20 Jun-20 Jul-20 Aug-20 Oct-20 Nov-20 Dec-20 Jan-21 Trend lecem 7 North West + North East and Yorkshire, 6.2 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 6.68 6.66 6.43 7.01 6.54 mm Midlands + East of England, 7.77 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 mm 7. 8 South East + South West 6.65 6.27 6.71 6.53 6.61 7.17 6.84 6.35 6.42 6.61 5.98 6.49 6.5 mm 6.5 6.33 6.79 6.32 6.9 6.36 6.44 6. 6.46 6.35 6.88 6. 9 London UNIDENTIFIED 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 be 2.49 2.54 2.4 2.6 2.47 mm 0 0 0. 0 0. 0 0 0 0 0.01 0. _____ 0. 0 0. 0 0. 0 0. 0. 0 0. 0. 0. 0. 23.08 1 Olonthly Subtotal Table 3 Total Quantity in millions by region 23.1 23.84 21.52 **▶**^{23.23} 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 23.25 22.54 24.52 11 Sep-20 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 Oct-20 Nov-20 Dec-20 Jan-21 Trend t-test (North vs. Total) 12 Jorth West + North East and Yorkshire, 0.8 ------1.11 1.03 1.12 1.12 1.23 1.2 1.24 1.33 1.25 1.32 1.25 1.4 1.25 1.57 1.53 1.39 1.42 0.82 0.74 $\nabla^{0.79}$ 0.79 0.77 0.84 9.99E-35 1.3 P-value

 1.
 2.05

 0.25
 0.26

 5.51
 5.32

 5.53
 5.91

 2.23 0 2.17 2.26 0.31 1 South East + South West 2.01 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 2.17 2.16 2.31 2.33 -----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 2.32 2.26 2.48 0.33 ------0.22 0.2 0.22 0.22 0.25 0.26 0.27 0.26 0.32 0.31 0.33 0 0 0 0 0 0 0 0 0 0 0 15^{Monthly Subtotal} Table 4 Actual Cost in £millions by region 4.51 4.23 4.64 4.62 5.09 4.91 5.11 5.47 5.54 5.59 5.5 5.96 5.68 ed from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 44

BMJ Open

Page 35 of 44

Su	nn	lementary	/ Table 5	 Methotrexate 	Ouantity (i	n millions)
201		iennenten j		in chief chate		

May-19

0.058 0.04 0.04 0.04 0.04 0.04 0.017 0.017

0.03 0.011 0.011 0.009 0.009 0.012 0.006

0.006 0.006 0.006 0.009 0.006 0.006 0.006 0.002 0.001 0.001 0.001

0.003 0.001

0. 0.001 0.001 0.001 0

0.001 0.001 0.001 0.001

0.059 0.041 0.041 0.04 0.04 0.04 0.018

0.018 0.032 0.01 0.01 0.009

0.006 0.006 0.006

0.006

0. 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001 0.001

0.001

4.05 4.05 4.064 0.064 0.044 0.043 0.043 0.043 0.02 0.02 0.02 0.011 0.011 0.011 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.000 0.002 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.002 0.001 0.001 0.002 0.001 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 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.000 0.002 0.002 0.002 0.002 0.002 0.001 0.001 0.001 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007

0. 0.001 0.001 0.001

0.001

n-19 3.928 0.055 0.055 0.037 0.037

0.036 0.036 0.016 0.035 0.01 0.035 0.01 0.008 0.008 0.008 0.003 0.005

0.005 0.005 0.006 0.006

0.000 0.006 0.006 0.003 0.001 0.001 0.003

0.

0. 0.001 0.001 0.001

0.001 0.001

Sum Total (Methotrexate)

Sum of top ten rows (10010: % Sum of top ten rows

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

4.253 97% 3.868 97% 4.187 4.116 97% 4.402 97% 4.061 97% 4.197 4.484 97% 4.143 97% 4.415 97% 4.228 97% 4.37 97% 4.374 97% 4.001 97% 4.662 97% 4.378 97% 4.187 97% 4.332 97% 4.52 97% 4.098 97% 4.416 97%

eb-19 ar-19

3.556 0.053 0.053 0.036 0.035 0.035 0.017 0.017 0.017 0.031 0.009 0.009 0.009 0.009 0.009 0.009

0.005 0.005 0.005 0.009 0.006 0.005 0.003 0.001 0.001 0.001 0.001 0.002

0.001 0.001 0.001

BNF CODE

BMJ Open

Oct-19

0.067 0.067 0.048 0.048 0.044 0.044 0.021 0.021 0.021 0.012 0.012 0.012 0.012 0.006 0.006 0.007 0.008 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005

0.072 0.072 0.051 0.051 0.049 0.049 0.022 0.022

0.028 0.012 0.012 0.011 0.011 0.012 0.007

0.007 0.007 0.008 0.008

0.009

0.006 0.005 0.002

0.001

0. 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001

Nov-19

3.826 0.07 0.05 0.05 0.045 0.045 0.045 0.022

0.026 0.013 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.008 0.005 0.005 0.003 0.001 0.001

0.002 0.001 0.002 0. 0.001 0.001 0.001 0.

0. 0.001 0.001 0.001 0.001 0.001 0.001

c-19
3.948
0.074
0.074
0.074
0.074
0.074
0.054
0.054
0.022
0.022
0.022
0.022
0.022
0.022
0.022
0.022
0.023
0.026
0.013
0.013
0.013
0.011
0.011
0.011
0.011
0.011
0.011
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
0.001
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
0.001
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
0.001
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 0.001 0.001 0.001

-20 3.949 0.075 0.075 0.053 0.048 0.048 0.023 0.023 0.023 0.023 0.023 0.023 0.013 0.011 0.011 0.011 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.015 0.015 0.015 0.015 0.015 0.053 0.048 0.023 0.023 0.013 0.011 0.011 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.05

ug-19

0.065 0.065 0.045 0.045 0.045 0.044 0.044 0.022 0.022 0.022 0.022 0.011 0.011 0.011 0.011 0.011 0.011 0.010 0.006 0.007 0.007 0.007 0.007 0.007 0.002 0.001 0.001 0.003 0.001 0.003 0.001

0. 0.001 0.001 0.001

0.001

0.069 0.048 0.046 0.046 0.046 0.021 0.021 0.013 0.01 0.013 0.007 0.009 0.006 0.005 0.005 0.002 0.001 0.001 0.001 0.001

0.001 0.001 0.001 0. 0.001 0.001 0.001

0.001 0.001

0.001

0.06 0.042 0.042 0.04 0.04 0.019 0.029 0.011 0.009 0.009 0.009 0.000 0.006 0.006 0.006 0.006 0.006 0.006 0.000 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001

3.608 0.07 0.07

0.049 0.049 0.046 0.021 0.021 0.022 0.012 0.011 0.011 0.011 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.007 0.002 0.001 0.002

0. 0.001 0.001 0.001 0.

0. 0.001

0. 0.001 0.001 0.001 0.001

r-20 3.934 0.079 0.079 0.056 0.056 0.052 0.052 0.023 0.023

0.023 0.014 0.014 0.012 0.012 0.012 0.012 0.009 0.009 0.009 0.008 0.008 0.008 0.008 0.008 0.008 0.005 0.005 0.005 0.002 0.002 0.002 0.002 0.002

0.001

0.001 0.001 0.001 0.001

4.195 0.083 0.083 0.06 0.054 0.054 0.055 0.015 0.015 0.013 0.013 0.013 0.013 0.003 0.008 0.006 0.008 0.008 0.008 0.000 0.002 0.002 0.002 0.002 0.002 0.002

0. 0.001 0.001 0.001 0 0. 0.001 0.001 0.001 0.

0.001

0.001 0.001 0.001 0.001 0.001

3.763 0.076 0.076 0.054 0.054 0.049 0.049 0.049 0.023 0.023

0.021 0.013 0.013 0.011 0.011 0.011 0.011

0.008 0.007 0.007

0.005 0.005 0.003

0.001 0.001 0.001 0.001 0.001 0.001

0.001

0. 0.001 0.001 0.001

►20 3.89 0.078 0.056 0.056 0.052 0.052 0.023 0.023 0.022 0.014 0.014 0.012 0.012 0.011 0.008

0.008 0.008 0.008 0.007 0.005 0.004 0.003 0.002 0.002 0.002 0.002 0.001 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

 1-20

 4.059

 0.082

 0.082

 0.082

 0.082

 0.082

 0.082

 0.054

 0.054

 0.054

 0.054

 0.054

 0.054

 0.054

 0.054

 0.054

 0.024

 0.024

 0.012

 0.012

 0.002

 0.006

 0.006

 0.007

 0.008

 0.009

 0.002

 0.002

 0.002

 0.002

 0.002

 0.002

 0.002

 0.001

 0.001

 0.001

 0.001

 0.001

 0.001

 0.001

 0.001

 0.001

 0.001

<u>we 20</u> 3.67 0.677 0.055 0.055 0.055 0.055 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.051 0.022 0.022 0.022 0.022 0.022 0.022 0.021 0.012 0.012 0.012 0.012 0.012 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0.006 0

0.001 0.001 0.001 0.001 0.001 0.001

3.958 0.082 0.082 0.082 0.066 0.066 0.054 0.054 0.054 0.054 0.015 0.015 0.015 0.013 0.013 0.013 0.013 0.019 0.009 0.008 0.008 0.008 0.008 0.008 0.0002 0.002 0.002

0.001 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

3.993 0.084 0.084 0.086 0.056 0.056 0.024 0.024 0.024 0.024 0.024 0.015 0.013 0.013 0.013 0.013 0.013 0.003 0.009 0.009 0.009 0.000 0.000 0.0001 0.001 0.001 0.001

Sup
Sup 1 2 3 4 5 6 7 BF DESCRIPTION Methotoreate Sing/2mi solution for injection vals Methotoreate 20m/20mi np pre-filed symptom 9 Methotoreate 20m/20mi np pre-filed symptom 9 Methotoreate 20m/20mi np pre-filed symptom 1 Methotoreate 20m/20mi
2
3
4 5
6
7 BNF DESCRIPTION Methotrexate 5mg/2ml solution for injection vials
8 Methotrexate 50mg/2ml solution for injection vials Methotrexate 1g/10ml solution for injection vials Methotrexate 20mg/0.8ml inj pre-filled syringes
9 Methotrexate 22.5mg/0.9ml inj pre-filled syringes Methotrexate 25mg/1ml inj pre-filled syringes Methotrexate 10mg/0.4ml inj pre-filled syringes
Methotrexate 12.5mg/0.5ml inj pre-filled syringes
Methotrexate 15mg/0.6ml inj pre-filled syringes Methotrexate 17.5mg/0.7ml inj pre-filled syringes Methotrexate 7.5mg/0.3ml inj pre-filled disposable Methotrexate 10mg/0.4ml inj pre-filled disposable
Methotrevate 12.5mg/0.5mi inj pre-filled disposable
Stehetorexate 17.5mg/0.7ml inj pre-filled disposabl Methotrexate 20mg/0.8ml inj pre-filled disposabl Methotrexate 22.5mg/0.9ml inj pre-filled disposabl Methotrexate 22.5mg/1ml inj pre-filled disposable de
1 Slatal 20mg/0.8ml solution for injection pre-fille latal 22.5mg/0.9ml inj pre-filled syringes
1 Gatal 10mg/0.4ml solution for injection pre-fille Zlatal 7.5mg/0.3ml inj pre-filled syringes
Zatal 12.5mg/0.5ml inj pre-filled syringes Zlatal 15mg/0.6ml solution for injection pre-fille Zlatal 17.5mg/0.7ml inj pre-filled syringes
 Bordimet 7.5mg/0.3ml solution for injection pre-fi Nordimet 10mg/0.4ml solution for injection pre-fi Pordimet 12.5mg/0.5ml solution for injection pre-fi
Available Total Standard Stand
Nordimet 22.5mg/0.9ml solution for injection pre-f 2 Nordimet 25mg/1ml solution for injection pre-fille Methotrexate 2.5mg tablets
22 Methotrexate 10mg tablets Alethotrexate 2.5mg/5ml oral liquid Methotrexate 5mg/5ml oral liquid
2 Stethotrexate 10mg/5ml oral liquid tethotrexate 7.5mg/5ml oral liquid
Methotrexate 12.5mg/5ml oral liquid dethotrexate 15mg/5ml oral liquid Methotrexate 20mg/2ml inj pre-filled syringes
2 Stethotrexate 15mg/1.5ml inj pre-filled syringes Methotrexate 7.5mg/0.15ml inj pre-filled syringes Methotrexate 10mg/0.2ml inj pre-filled syringes
Green Straight Comparison of the straight C
2 Methotrexate 25mg/0.5ml inj pre-filled syringes Methotrexate 30mg/0.6ml inj pre-filled syringes Methotrexate 12.5mg/0.25ml inj pre-filled syringes
Methotrexate 22.5mg/0.45ml inj pre-filled syringes 2 Stehotrexate 17.5mg/0.35ml inj pre-filled disposable Methotrexate 20mg/0.4ml inj pre-filled disposable
Methotrexate 22.5mg/0.45ml inj pre-filled disposab Methotrexate 7.5mg/0.15ml inj pre-filled disposabl Methotrexate 27.5mg/0.55ml inj pre-filled disposab
3 Methotrexate 30mg/0.6ml inj pre-filled disposable Methotrexate 25mg/0.5ml inj pre-filled disposable Methotrexate 15mg/0.3ml inj pre-filled disposable
 Methotrexate 12.5mg/0.25ml inj pre-filled disposab Methotrexate 10mg/0.2ml inj pre-filled disposable Diethotrexate 2mg/ml oral solution sugar free
3 Anaxtrex 2.5mg tablets Maxtrex 10mg tablets 3 4 etoject 20mg/2ml solution for injection pre-fille
Metoject 10mg/1ml solution for injection pre-fille Metoject 15mg/1.5ml inj pre-filled syringes Metoject 7.5mg/0.15ml inj pre-filled syringes
Metoject 7.5mg/0.15ml inj pre-filled syringes Metoject 10mg/0.2ml inj pre-filled syringes Metoject 15mg/0.3ml inj pre-filled syringes
37 letoject 20mg/0.4ml inj pre-filled syringes
Metoject 25.mg/0.5ml inj pre-filled syringes Metoject 12.5mg/0.25ml inj pre-filled syringes Metoject 22.5mg/0.45ml inj pre-filled syringes
3 Stetoject PEN 17.5mg/0.35ml inj pre-filled pens Metoject PEN 17.5mg/0.35ml inj pre-filled pen Metoject PEN 20mg/0.4ml inj pre-filled pens
 A Detoject PEN 20mg/0.4m inj pre-filled pen Metoject PEN 22.5mg/0.45m inj pre-filled pen Metoject PEN 22.5mg/0.45m inj pre-filled pen A Metoject PEN 25.5mg/0.15m inj pre-filled pen
Metoject PEN 7.5mg/0.15ml inj pre-filled pens Dietoject PEN 27.5mg/0.55ml inj pre-filled pens
Metoject PEN 27.5mg/0.55ml inj pre-filled pen 4 Sletoject PEN 30mg/0.6ml inj pre-filled pens Hetoject PEN 30mg/0.6ml inj pre-filled pen
Metoject PEN 25mg/0.5ml inj pre-filled pens detoject PEN 25mg/0.5ml inj pre-filled pen Metoject PEN 15mg/0.5ml inj pre-filled pen
Sletoject PEN 15mg/0.3ml inj pre-filled pens Sletoject PEN 12.5mg/0.25ml inj pre-filled pens Metoject PEN 12.5mg/0.25ml inj pre-filled pen
4 Gretoject PEN 10mg/0.2ml inj pre-filled pens Metoject PEN 10mg/0.2ml inj pre-filled pen
4 Trethofill 17.5mg/0.15ml inj pre-filled injector Methofill10mg/0.2ml inj pre-filled injector Methofill 15.5mg/0.3cml inj pre-filled injector
4 Settodil 12.5mg/0.3ml inj pre-filed injector Methofil 13.5mg/0.3ml inj pre-filed injector Methofil 12.5mg/0.35ml inj pre-filed injector 4 Settofil 12.5mg/0.45ml inj pre-filed injector
Methofill 25mg/0.5ml inj pre-filled injector 5 (Nethofill 27.5mg/0.55ml inj pre-filled injector
5 1 Methofill 10mg/0.2ml inj pre-filled syringes
Methofill 17.5mg/0.35ml inj pre-filled syringes 2 hethofill 20mg/0.4ml inj pre-filled syringes Methofill 22.5mg/0.45ml inj pre-filled syringes
5 Stethofill 25mg/0.5ml inj pre-filled syringes Stethofill 12.5mg/0.25ml inj pre-filled syringes
54
55 56
57

- 59
- 60

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

v-20

0.081 0.059 0.059 0.053 0.053 0.053 0.023

0.017 0.017 0.014 0.013 0.013 0.013 0.011 0.009 0.008 0.008 0.008 0.008 0.008 0.008 0.008 0.008 0.008 0.008 0.002 0.002 0.002 0.001 0.001 0.001 0.001 0.001

0. 0.001 0.001 0.001 0.001

4.299 97% 4.68 97% 4.299 97%

4.459 97%

0. 0.001 0.001 0.001 0.001

0.064 0.064 0.058 0.058 0.025 0.025

0.02 0.016 0.016 0.014 0.014 0.014 0.011 0.009

0.009

0.004 0.004 0.003

0.002

0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001

18-14 18-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19-14 19

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstr	act			Decer	
	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 		RECORD 1.1: The type of ata used should be specified in the title or abstract. When possible, the name of the databases use should be included.	Title and abstra PG 2
		summary of what was done and what was found	Pr re	RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Title and abstra PG 2
			6	RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	N/A
Introduction				h April	
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		April 23, 2024 by guest.	In Introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses		st. Protected by copyright	End of Introduction section (pg 5)
Methods				CO P	
Methods		For peer review only - ht	tp://bmjopen.bmj.com/site		

BMJ Open

 Page 38 of 44

			BMJ Open	36/bmjc	Page 38
Study Design	4	Present key elements of study design early in the paper		pen-2021-05	Materials and methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		936 on 23 Decemb	Materials and methods section
				er 2022	
Participants	6	 (a) Cohort study- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i>- 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 <i>Cross-sectional</i> <i>study</i>- 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

Page	39	of	44
------	----	----	----

ige 39 of 44			BMJ Open	36/bmjop	
		<i>Case-control study-</i> For matched studies, give matching criteria and the number of controls per case		3en-2021-051936	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete fist 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	ev.e	://bmjopen.bmj.com/ on April 23, 2024 by g	Materials and methods section. Original data are available from <u>https://www.nhsbs</u> <u>a.nhs.uk/prescripti</u> <u>on- data/prescribing- data/english- prescribing-data- epd</u>
, L				Jest	·
Bias	9	Describe any efforts to address potential sources of bias		Protected by copyright	N/A
 3 4 5		For peer review only - htt	tp://bmjopen.bmj.com/site/	/about/guidelines.xhtml	

			BMJ Open	36/bmjop	Page
Study size	10	Explain how the study size was arrived at		pen-2021-	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		051936 on 23 Decer	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 		nber 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by gu	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

Page 4	1 of 44			BMJ Open	36/bmjopen-2	
2 3 4 5 6 7					RECORD 12.2: Authors should provide information on the data cleaning methods used the study.	Materials and methods section
8 9 10 11 12 13 14 15 16 17	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.
17 18 19	Results	·		24	d from	
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, 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 	ierie	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , 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
34 35 36 37 38 39 40 41 42 43 44 45 46			For peer review only - ht ^r	tp://bmjopen.bmj.com/site/	y guest. Protected by copyright. /about/guidelines.xhtml	

				BMJ Open		36/bmjo	Page 42 o	of 44
1 2 3 4 5 6 7 8 9 10 11 12 13	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) <i>Cohort study</i>- summarise follow-up time (e.g., average and total amount) 			36/bmjopen-2021-051936 on 23 December 2022. D	Results, Table 1	
14 15 16 17 18 19 20 21 22	Outcome data	15	<i>Cohort study-</i> Report numbers of outcome events or summary measures over time <i>Case-control study-</i> Report numbers in each exposure			Downloaded from http://bmj	Results, Table 1	
23 24 25				- Vio		open.bn		
26 27 28 29 30 31			category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		201/	nj.com/ on April 23,		
32 33 34 35 36 37 38 39 40 41 42 43						, 2024 by guest. Protected by copyright		
44 45 46			For peer review only - htt	tp://bmjopen.bmj.com/site/	/about/guidelines.xhtml	h.		

Page 4	3 of 44			BMJ Open		36/bmio	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28	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			36/bmiopen-2021-051936 on 23 December 2022. Downloaded frbm http://bmiopen.bmi.com/ on April 23	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	revie	200	pm http://bmjopen.bmj.com/ on A	Results section. Supplementary - ARIMA Syntax Supplementary - Sensitivity analysis
29 30 31	Discussion	•				April 23	
32 33 34 35	Key results	18	Summarise key results with reference to study objectives			, 2024 by gu	Discussion section
36 37 38 39 40 41 42 43 44 45 46 47			For peer review only - ht	tp://bmjopen.bmj.com/site,	/about/guidelines.xhtml	est. Protected by copyright.	

			BMJ Open		36/bmjoj	Page 44
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 t implications of using data not created or collected to specific research question discussion of misclassific unmeasured confounding data, and changing eligibit time, as they pertain to the being reported.	(agat were bganswer the (agat Include agon bias, missing Iffy over	Discussion section
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			2022. Down	Discussion section
		DO			oaded	
		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	rev:		from http://bmjop	
Generalisability	21	Discuss the generalisability (external validity) of the study results	0	2	en.bmj.com/	Discussion section
Other Information	on			5	on Apri	
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			l 23, 2024 by guest. P	Acknowledgment section
		For peer review only - ht	tp://bmjopen.bmj.com/site/	/about/guidelines.xhtml	notected by copyright.	

Page 45 of 44				36/bmjop		
1 2 3 4 5 6 7	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 program code.	ARIMA Syntax
$\begin{array}{c} 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ \end{array}$	Committee. The RE in press.	porting		ational Routinely-collect	ted health Data (RECORD) State: Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright	ment. PLoS Medicine 2015;