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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 with after the first lockdown.

Results Fluctuation in monthly medicines use is noted in March 2020: a jump is observed for hydroxychloroquine (Mann-Whitney, $SE = 14.652$, standardised test statistic 1.911, p value=0.059) over the study period. After the first lockdown, medicines use fluctuated, with wide confidence intervals. Unit-cost prices changed substantially: sulfasalazine 33% increase, hydroxychloroquine 98% increase, azathioprine 41% increase, methotrexate 41% increase, leflunomide 20% decrease. London showed the least quantity variance, suggesting more homogeneous prescribing and patient access compared with 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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a first of its kind work using autoregressive integrated moving average 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.



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patients on these medicines and assess their prescription-day coverage, with planned actions to flag and follow-up adherence concerns in patients.

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 1948² and reimburses primary-care contractors (eg, 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 such as sulfasalazine, hydroxychloroquine sulfate, azathioprine, methotrexate, leflunomide are the mainstay for the treatment of many painful conditions of the joints, for example, rheumatoid arthritis (RA), psoriatic arthritis, systemic lupus erythematosus, spondyloarthritis and related arthritic conditions.⁵⁻⁹ Among the most common are RA, Crohn's disease and psoriasis that affect 0.8%,¹⁰ 0.395% (overall adult prevalence of 403 per 100 000 population in 2017¹¹) and 2.8%¹² of the UK population, respectively. A 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 with the general population: RA (aRR 1.2, 1.1–1.3). While, other IMIDs such as 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.

RA is a chronic systemic autoimmune disease that primarily targets synovial joints, resulting in pain and functional limitations¹⁴ 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 bowels¹⁹⁻²¹ (eg, Crohn's disease, ulcerated colitis, diverticulitis) as well as for antirejection therapy²² when organ transplants or grafts have been used as they suppress 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 (eg, cyclophosphamide), Janus kinase inhibitors (eg, baricitinib), phosphodiesterase type-4 inhibitor (eg, apremilast) and tumour necrosis factor—alpha inhibitor (eg, 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 among 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 three times more likely to have had a reduction in household family income than either individuals with osteoarthritis or those without arthritis.²⁹⁻³³ In this way, the economic effects of RA are staggering and emphasise the importance of early recognition and treatment.³⁴ A recent 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 UK, during the pandemic, patients could not see healthcare professionals in a timely fashion, leading to backlogs even till today including operations, cancer waiting, GP referrals and casualty waiting times, with some people waiting over 1 year for minor operations.³⁶ The government has outlined how it has learnt 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 before⁴¹⁻⁴³ the pandemic and after for many medications during the pandemic (eg, ibuprofen and paracetamol). The European Medicines Agency acknowledges shortage of etanercept (Enbrel) in prefilled 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, for example, 0105010E0AAABAB for 'Sulfasalazine 500 mg gastroresistant tablets' to maintain patient confidentiality. This data set contains the following variables, among others: 'YEAR_MONTH', for example, presented as 201901 to represent Jan-19, 'CHEMICAL_SUBSTANCE', for example, methotrexate, sulfasalazine, 'Chemical Substance' by code, for example, 1001030U0, 'BNF_DESCRIPTION', for example, Metoject PEN 20 mg/0.4 mL inj prefilled pens; sulazine EC 500 mg tablets (Genesis Pharm), related 'BNF_CODE', for example, 1001030U0BEARBW, 'REGIONAL_OFFICE_NAME', for example, East Anglia Area, Wessex Area, North Of England, 'STP_NAME', for example, 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 (eg, tablets, prefilled insulin pens) and 'actual cost' for reimbursement. In the EPD, there is approximately a latency of released data by 2 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 (eg, 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 (eg, sulfasalazine suppositories) were excluded as well as all cutaneous products (eg, creams, gels, medicated plasters, sprays, cutaneous solutions, transdermal patches, topical solutions). Hence, the data contains tablets, oral liquids and injectables (prefilled 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, that is, 333 459 762 rows of data (99 gigabytes of data) were extracted using Then, these were filtered down to the specific medications under study. Each row represents an aggregated amount of that medication supplied at the GPs' 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 file were imported into a Microsoft SQL server table labelled EPD. As each one was imported, it was validated and assigned an exact data type (eg, '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 (eg, that text characters were not 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 packages that imported, validated and consolidated the data within an automated import routine. Detailed methods have been previously published⁴⁶ 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 23 March 2020, a second lockdown commenced on 5 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 trends⁴⁷ at the 95% confidence level.

A commonly used time series modelling framework (autoregressive integrated moving average (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 14 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 point⁵¹ was used). The estimates for the difference in prescription total quantity as at March 2020, and also the difference in the linear trend (ie, 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

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

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

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), upper (UCI) and lower (LCI) 95% confidence intervals.

LCI, 95% lower confidence intervals; SD, Standard Deviation ; UCI, 95% upper confidence intervals.

conducted using changepoint^{52 53} and binary segmentation analysis.⁵¹ See ARIMA Syntax in online supplemental table 1. See sensitivity analysis in online supplemental 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 This data set is covered by the OGL 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.

By total quantities of medicines

Since the March lockdown, fluctuations in monthly volumes are observed. See online supplemental table 3 for fluctuating total quantities of antirheumatics' 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, SE 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.

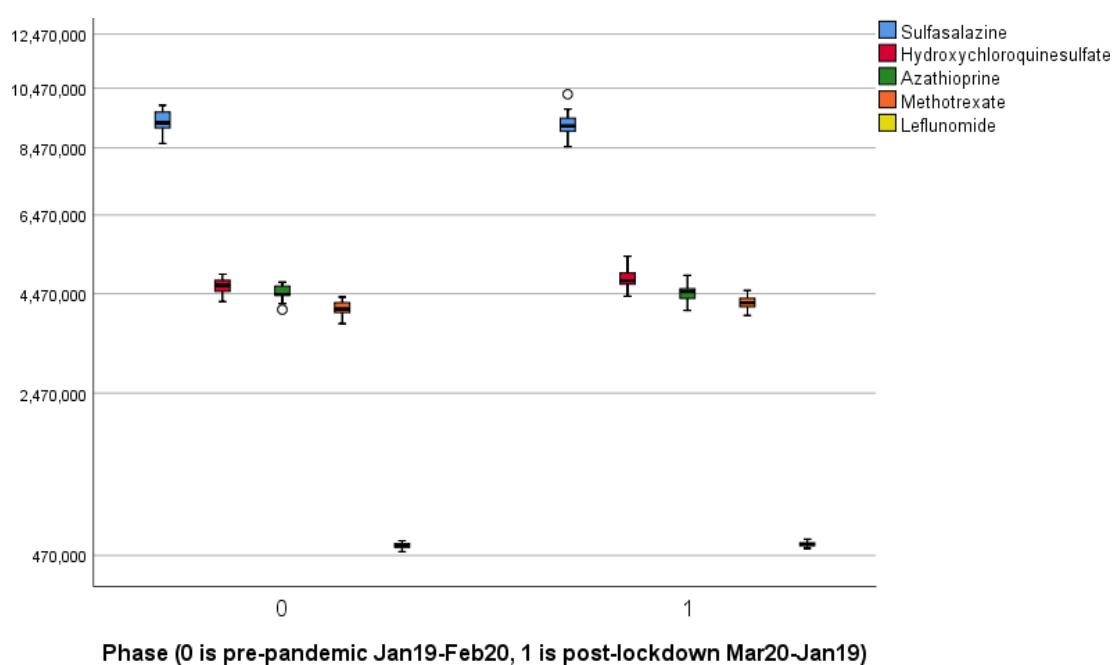


Figure 1 Box plot representing values before the pandemic and after its onset. Quantities are presented in absolute numbers.

Supplemental material (online supplemental table 3—quantity and cost) shows that there was a substantial increase in unit cost of medication during this study period as indicated by the analysis below:

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

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

ITS (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**.

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 CIs 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 with 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 ITS 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 CI bounds that do definitely show a shift

Table 2 Estimated change in prescription volumes at March 2020 without autoregression autoregressive integrated moving average (0,0,0)

	Parameter estimate	SE	T statistic	P value	Lower CI	Upper CI
Estimated slope (per month) before March 2020						
Sulfasalazine-Model_1	5435	28 871	0.188	0.852	-54 151	65 021
Hydroxychloroquine sulfate-Model_2	-10 955	14 336	-0.764	0.453	-40 543	18 632
Azathioprine-Model_3	-12 052	12 273	-0.982	0.337	-37 382	13 278
Methotrexate-Model_4	7966	11 836	0.673	0.508	-16 462	32 395
Leflunomide-Model_5	561	1662	0.338	0.739	-2870	3992
Post versus pre effect (step change)						
Sulfasalazine-Model_1	659 017	875 894	0.752	0.46	-1 148 740	2 466 774
Hydroxychloroquine sulfate-Model_2	814 729	434 936	1.873	0.075	-82 935	1 712 394
Azathioprine-Model_3	786 705	372 342	2.113	0.047	18 229	1 555 182
Methotrexate-Model_4	249 614	359 099	0.695	0.495	-491 531	990 758
Leflunomide-Model_5	30 388	50 436	0.603	0.553	-73 706	134 482
Estimated slope (per month) after February 2020						
Sulfasalazine-Model_1	-38 151	50 570	-0.754	0.459	-142 522	66 220
Hydroxychloroquine sulfate-Model_2	-24 392	25 111	-0.971	0.342	-76 219	27 434
Azathioprine-Model_3	-31 340	21 497	-1.458	0.16	-75 708	13 028
Methotrexate-Model_4	-10 634	20 733	-0.513	0.613	-53 424	32 156
Leflunomide-Model_5	-1188	2912	-0.408	0.687	-7198	4822

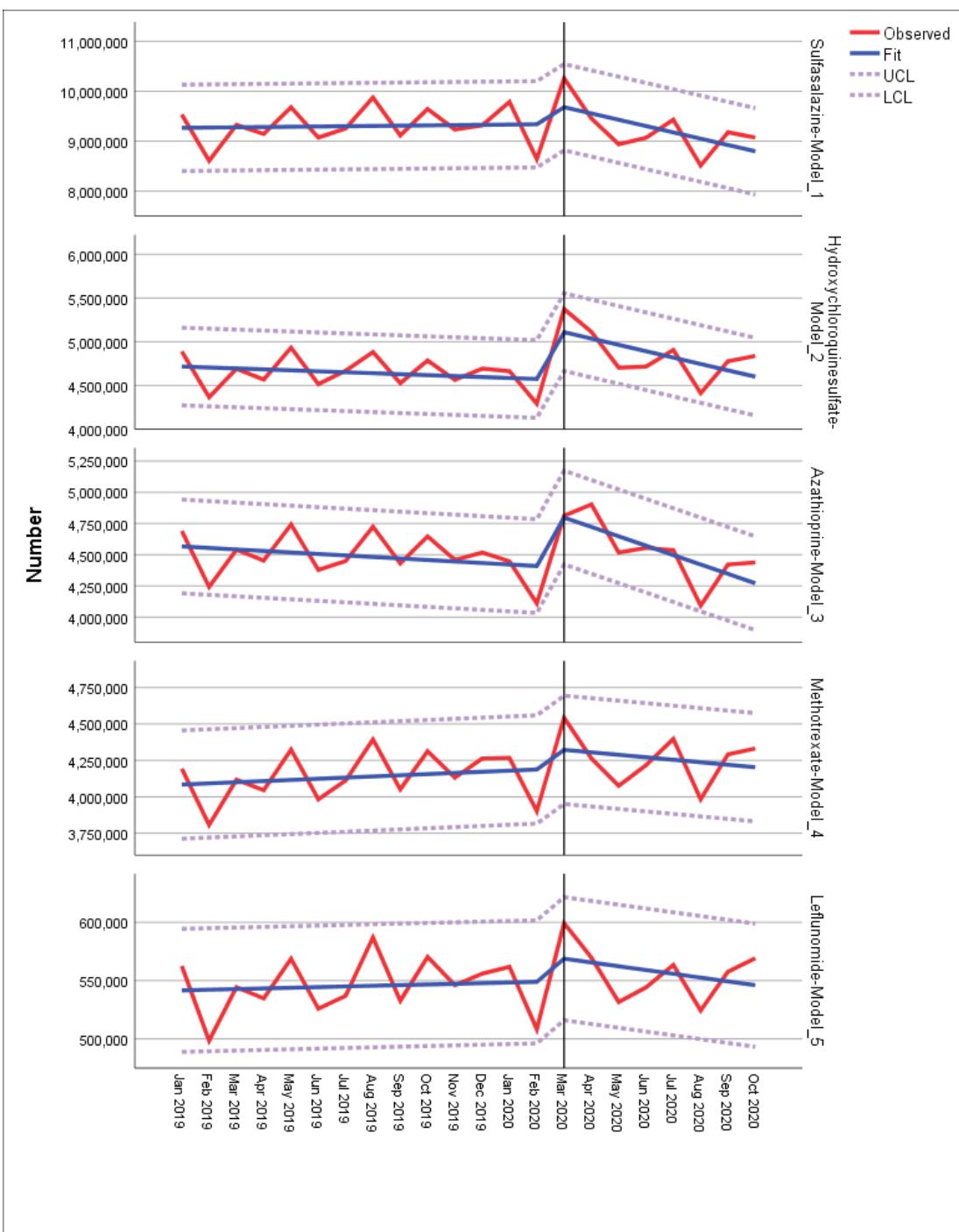


Figure 2 Autoregressive integrated moving average (0,0,0)(0,0,0) prescription volumes for individual medicines: sulfasalazine; hydroxychloroquine sulfate; azathioprine; methotrexate; leflunomide. Upper (UCL) and lower (LCL) 95% confidence intervals.

downwards after the March 2020 interrupt point with CIs becoming more negative than before.

Online supplemental 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 (ie, 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.

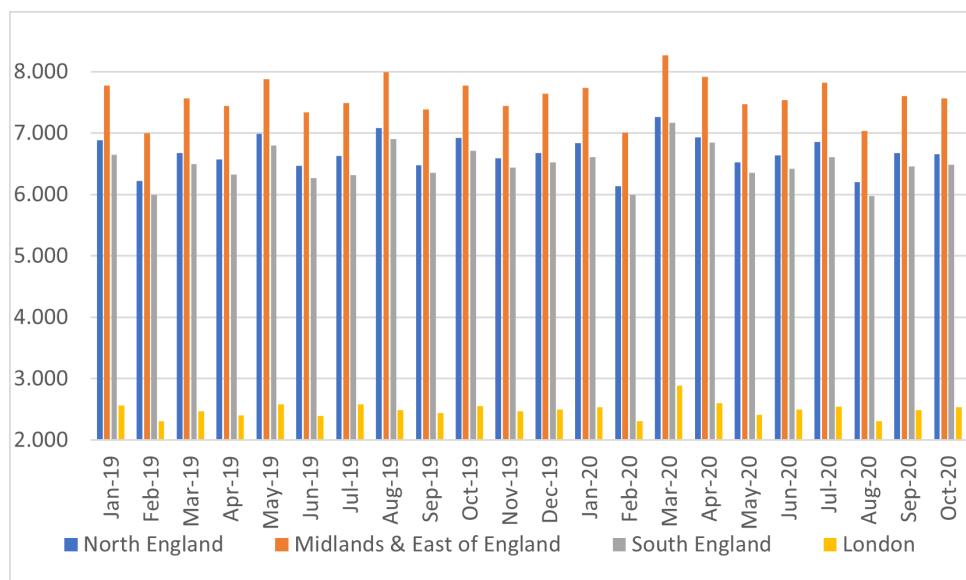


Figure 3 Monthly regional distribution (higher March and lower May 2020 quantities of rheumatoid arthritis medicines are presented in the callouts).

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 online supplemental 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, SD) 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 (online supplemental 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 ITS 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 price 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, for example, 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 1 year for treatment compared with 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 (eg, 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. Healthcare 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. (See online supplemental video 1, for a 3-minute rapid summary)

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Contributors 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. RaB is responsible for the overall content as the guarantor. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the

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