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Title

Inhalation corticosteroids for COVID-19 – a real world data analysis on guideline adherence

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Abstract

Background

The recommendation to consider prescribing inhalation corticosteroids to a subgroup of vulnerable COVID-19 patients was added to the Dutch medical guideline on November 11, 2021, and was also adopted by other countries during the pandemic.

Aim

To evaluate the adherence of general practitioners to this guideline, and whether real-world data quality is sufficient to study the effect of revised guidelines on prescribing behaviour.

Design and Setting

A retrospective cohort study using Dutch primary care data from the Extramural LUMC Academic Network database, containing patient data of 129 general practices in the Leiden – The Hague area.

Method

We performed an interrupted time series analysis to measure the effect of the new guideline on the prescription rate of ICS, accounting for general trend and seasonal fluctuations.

Results

Between July 1, 2020 to August 1, 2022, 131,482 patients had 164,098 COVID-19 consultations. During this period, 1,709 patients received 2,094 ICS prescriptions for COVID-19. After the guideline update, there was an instantaneous decrease in prescription rate (IRR 0.47, 95% CI 0.32-0.69). Prescription rate in the subgroup of vulnerable patients did not change significantly (IRR 0.93, 95% CI 0.66-1.32), while less vulnerable patients were significantly prescribed less (IRR 0.29, 95% CI 0.14-0.59).

Conclusion

The revision to COVID-19 guidelines had significant impact on general practitioners' prescription behaviour soon after publication: prescription rate remained constant for vulnerable patients, while less vulnerable patient were significantly prescribed less often. Using electronic health records it is feasible to assess changes in guideline adherence using interrupted time series.

Keywords:

General practice, COVID-19, Interrupted Time Series Analysis, Guideline Adherence, Electronic Health Records

How this fits in:

While guideline adherence is not a new research topic, the effect of revisions to guidelines have not been studied widely. The method of interrupted time series is a natural way to assess changes in guideline adherence when revisions are made. We found that electronic health record quality is sufficient to study the effect of the Dutch COVID-19 guideline update to prescribe inhalation corticosteroids.

List of abbreviations:

EHR: electronic health records

ICS: inhalation corticosteroids

IRR: incidence rate ratio

CI: confidence interval

NHG: Nederlands Huisartsen Genootschap (Dutch College of General Practitioners)

ELAN: extramural LUMC academic network

GP: general practitioner

ICPC: international Classification of Primary Care

ATC: anatomical Therapeutic Chemical

SD: standard deviation

Introduction

During the COVID-19 pandemic, relatively few patients with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease were hospitalized. This was in contrast to expectations, as these patients were more susceptible to a COVID-19 infection and would have had a higher mortality than patients without comorbidities.[1] Patients with chronic respiratory disease are frequently prescribed inhaled corticosteroids (ICS) such as budesonide.[2,3] It was hypothesized that ICS protect patients against severe COVID-19, leading to several randomized clinical trials evaluating the effect of ICS on COVID-19 susceptibility, severity and mortality. It was found that inhaled budesonide reduces the time to recovery after COVID-19 in patients with chronic lung disease.[4–7]

After considering the aforementioned evidence, healthcare organisations in several countries recommended budesonide as a treatment for COVID-19. This recommendation had been adopted in medical guidelines in India, Russia, Saudi Arabia and British Colombia in Canada, among others.[8–11] In the Netherlands, the Dutch College of General Practitioners (NHG) updated their COVID-guideline on November 2, 2021, issuing a recommendation for general practitioners to consider prescribing budesonide to older patients with recent symptoms, insufficient vaccine protection and/or comorbidities. Before the guideline update, there was no recommendation regarding budesonide or other ICS for COVID-19 patients. The guideline update was highlighted in the NHG newsletter the same week.

After randomized clinical trials provide new evidence, the step to translation, incorporation and implementation of this new evidence into new guidelines and recommendations is often a slow process.[12] Furthermore, it remains the question whether new guidelines are followed, which could be a deliberate choice by clinician or patient, or due to unfamiliarity to the latest recommendations. Research using real-world data is essential to assess whether guidelines are being followed.[13,14]

This study aims to analyse the change in prescription rate for budesonide and other ICS after the guideline update for two reasons. First, to observe whether- and to which extent ICS have been prescribed to COVID-19 patients after guideline revision. Second, to assess whether current real-world data quality is sufficient to study changes in prescribing behaviour.

Methods

Data source and patient population

We used electronic health records collected by general practitioners affiliated with the Extramural LUMC Academic Network (ELAN), Leiden, the Netherlands.[15] The ELAN data warehouse contains anonymized data including patient characteristics, consultations and medication prescriptions from patients living in the urban cities of Leiden, the Hague and Zoetermeer and the surrounding suburban and rural areas. In 2021, 572.930 patients out of the total 1.719.617 individuals in this region (33%) were registered with one of the ELAN general practitioners (GP).[16] Diagnoses and symptoms of consultations are coded according to International Classification of Primary Care (ICPC).[17,18] Medication is coded according to Anatomical Therapeutic Chemical (ATC) classification.[19]

Our study population consisted of all patients enlisted with ELAN general practitioner centres who had at least one consultation (ICPC R83 or R83.03) for COVID-19 within the period of July 1, 2020, and August 1, 2022. Initially, R83 was used to classify COVID-19 cases before the specific code R83.03 was available.[20,21] We extracted budesonide prescriptions (ATC R03BA02), as well as other glucocorticoids (ATC R03BA*) and corticosteroids in combination with adrenergics or other drugs (ATC R03AK*).

According to the Dutch College of General Practitioner's (NHG) guideline from November 2, 2021 onwards, COVID-19 patients were eligible for budesonide if (i) they had symptoms for less than 14 days; (ii) have not been fully vaccinated, are vaccinated but considered a non-responder, or vaccinated but developed moderate to severe complaints; (iii) and are at least 65 years old or at least 50 years old and have at least one of the following comorbidities: (severely) reduced immune system, (severe) chronic kidney damage, cardiovascular disease, diabetes mellitus, COPD, cirrhosis of the liver and morbid obesity.[22] Information on symptom duration, vaccinations and obesity status

were unavailable in the ELAN database. ICPC codes of comorbidities are given in Supplementary Table 1.

Approximately 25% of prescriptions were coupled to a diagnosis. Thus, for the majority of ICS prescriptions we could not determine with certainty whether this was prescribed for COVID-19 or for chronic respiratory diseases. Therefore, we assumed that any ICS prescription within 14 days of a COVID-19 consultation was prescribed for this reason.

To preserve patient privacy, the ELAN data warehouse only provides birth year, rather than birth date. Patient age was estimated by assuming a birth date of July 2 in the birth year. All other required variables were complete.

Study Design and Statistical Analysis

We used an interrupted time series design to assess ICS prescription rate for COVID-19 patients before and after the guideline was published. Our methodology adhered to recommendations outlined in Lopez et al., 2016.[23] For the time series, we extracted the number of COVID-19 consultations with ICS prescription and the total number of COVID-19 consultations in every week of the study period, from which we determined the weekly rate of prescription. The interruption was set as the day the COVID-19 guideline was updated to include the advice on budesonide, on 2 November, 2021. The study included 70 weeks of pre-intervention data and 39 weeks of post-intervention data.

To estimate the effect of the interruption on the prescription rate, we fitted a quasi-Poisson model to the weekly counts of COVID-19 episodes, with the weekly total COVID-19 episodes included as offset. We included a dummy variable which is 0 in the weeks before the guideline update, and 1 afterwards. Seasonal fluctuations were accounted for by including dummy variables for the year quarters in the model. The trend over the study period and trend change was modelled with variables indicating the number of weeks since the start of the study and the number of weeks since

the update (equal to 0 before update). We adjusted for over-dispersion by scaling the standard errors with a quasi-Poisson model.[23] We tested for auto-correlation using the Durbin Watson test, and compensated for any auto-correlation by scaling the standard errors of the model with the Newey-West method.[24] The model formula is specified in the Supplementary materials.

The effect of the interruption was estimated by incidence risk ratio's (IRR) with 95% confidence interval for the instantaneous difference and the difference in trend of the prescription rate. The IRR represents the ratio of the predicted prescription rate for one unit increase in the corresponding covariate, holding other variables constant.

Data management and analysis was done in R version 4.3.3 and packages data.table, lubridate, ggplot2, table1, car, lmtest, and sandwich [25–32].

Sensitivity and subgroup analysis

As a sensitivity analysis, we fitted the model on the overall study population without correcting for seasonal effects. To perform a subgroup analysis, patients were grouped by whether they satisfied criterion (iii) as given by the NHG or not. That is, patients of 65+ years old or 50+ with comorbidity were categorized as vulnerable patients, all other patients were categorized as less vulnerable patients.

Results

Between July 1, 2020 and August 1, 2022, 131,482 patients together had 164,098 COVID-19 episodes. The mean age of a patient during their first COVID-19 episode was 36.8 years (SD: 20.5) and 60,623 (46.1%) subjects were male.

The baseline characteristics of patients that had at least one COVID-19 consultation during the study period are presented in Table 1. There were no significant differences between the patients that were prescribed ICS before and after the guideline revision. Patients who were prescribed inhalation corticosteroids were more often female, older, with comorbidities and experienced more distinct COVID-19 episodes, compared to patients that were not prescribed these medications ($p < 0.001$ for all comparisons).

During the study period, 1,709 patients received a total of 2,094 inhalation corticosteroid prescriptions following a COVID-19 episode. Budesonide was prescribed 260 times (0.2% of COVID-19 episodes), other glucocorticoids were prescribed 762 times (0.5%), and corticosteroids in combination with adrenergics or other drugs were prescribed 1,072 times (0.7%).

In Figure 1, the weekly amount of COVID-19 consultations and weekly consultations with ICS prescription are shown, along with a vertical line indicating the moment when the guideline started recommending prescribing inhalation corticosteroids.

In Table 2, and more extensively in Table S2, the results of the fitted quasi-Poisson model are presented. We found a statistically significant decrease in the weekly rate of inhalation corticosteroid prescriptions for COVID-19 consultations after publication of the guideline (IRR 0.47, 95% CI 0.32-0.69). There was no significant trend during the study period (IRR 1.00, 95% CI 1.00 – 1.01) and no significant trend change after the updated guideline (IRR 1.01, 95% CI 0.99 – 1.02). Thus, after adjusting for overall trend and seasonal effects, the prescription rate is reduced by a factor of 0.47 after guideline revision. The results of the Durbin Watson test, shown in Table S3,

shows there is minor but significant autocorrelation, for which we adjusted the standard errors and confidence intervals using the Newey-West method.

In Figure 2 the weekly rate of COVID-19 cases with ICS prescription per COVID-19 case is presented, along with the model fit and counterfactual trend, which is determined by extending the pre-intervention trend into the post-intervention period. [33]

Our sensitivity analysis shows that the effect without adjusting for the seasonal effects is similar (Table S4), but due to higher autocorrelation (table S5) the confidence interval is larger.

We did not detect an instantaneous change in prescription rate for the subgroup of vulnerable patients (IRR 0.93, 95% CI 0.66-1.32), while the prescription rate was significantly decreasing per week after guideline revision (IRR 0.98, 95% CI 0.96 – 0.99). In the subgroup of less vulnerable patients we found an instantaneous significant decrease in prescription rate (IRR 0.29, 95% CI 0.14 - 0.59), while afterwards the rate increases per week (IRR 1.04 95% CI 1.01 - 1.07). See also Supplementary Tables S6 and S8. In Supplementary Tables S7 and S9 , we report the results of the Durbin Watson tests for the subgroup analyses, which again indicate minor but significant autocorrelation.

Discussion

Summary

We found a decrease in the inhalation corticosteroids prescription rate for COVID-19 infection after the guideline update, with no significant trend or trend change. The subgroup of vulnerable patients showed a gradual decrease in prescription rate after guideline revision. In the subgroup of less vulnerable patients there was a strong instantaneous decrease in prescription rate, followed by a gradual increase.

Several factors may explain the decrease in overall prescription rate after the guideline change. The NHG advised prescribing to a specific subgroup of patients, leading to fewer ICS prescriptions in patients outside this group. Our subgroup analysis confirms this result. Another possible reason for the overall decrease in prescription rate, is because it is a weak recommendation, which means that GPs can consider prescribing.

The extraordinary circumstances of the early phase of the pandemic may have caused general practitioners to prescribe medication more frequently despite limited evidence. As COVID-19 knowledge increased, general practitioners may have changed to a more cautious approach, decreasing the prescription rate compared to the early phase.

The wave of COVID-19 cases that took place immediately after the guideline update (November 2021) may also have decreased the prescription rate. Due to increased COVID-19 consultations, general practitioners became more overloaded with work and had less time per patient.[34,35] To properly instruct patients on how to use inhalers, GPs would need to see them face to face. There may have been a higher proportion of remote consultations during this wave, which would lower the opportunities to prescribe ICS. Additionally, patients were having relatively milder symptoms in the later stages of the COVID pandemic, due to higher vaccination rates and less severe COVID-19 variants.[36–38]

It seems paradoxical that prescribing behaviour shifted opposite to the recommendation: instead of an increase, the guideline led to an overall decrease in prescriptions. However, subgroup analysis shows the reduction mostly occurred in the group for which the advice is to not prescribe. Thus, we can conclude that GPs followed the guidelines accurately.

Comparison with existing literature

In this study we observed the GP prescription behaviour after a guideline change, supported by evidence from two randomized clinical trials. In the PRINCIPLE trial, 1,073 COVID-19 patients aged 65+ years or 50+ years with comorbidities were randomized to budesonide between November 27, 2020, until March 31, 2021.[7] In our population, only 42% of the ICS-prescribed patients fell in this category; they tended to be younger and often without comorbidities. The STOIC trial, with 73 participants assigned to budesonide between July 16 and December 9, 2020, had no specific restrictions on patient characteristics.[6] The patients of STOIC are similar to the population in our study. Since our study period lasted from July 1, 2020 to august 1, 2022, it is likely that during certain periods, different COVID-19 variants were dominant compared to the dominant variants of the PRINCIPLE and STOIC trial. Milder variants may have reduced the need for prescribing ICS.

Previous studies have used real-world data to monitor guideline adherence. For example, natural language processing algorithms have been employed on clinical notes of asthma patients to assess adherence to asthma guidelines, and a web-based dashboard monitored endometrial cancer guideline adherence using a national registry.[39,40] As another example, COPD guideline adherence, especially regarding ICS therapy, was studied using data from 900 general practitioners in Italy.[41] Splitting the study period in 4 different cohorts allowed to assess changing adherence. Thus, monitoring guideline adherence is feasible with real world data and various studies have already done so.

Strengths and limitations

This is the first study that estimated the adherence to the revised guideline of COVID-19 with respect to prescribing ICS. The strength of our study lies in the use of real world data of a large number of COVID-19 patients. Our methods and results can be used for future updates of guidelines, not only for COVID-19 but for a wide range of diseases and their guidelines.

A segmented Poisson regression for an interrupted time series design is a scientifically valid method to quantify the effect of changes in guidelines. Its advantage over other methods lies in its relatively simple application with interpretable results, and possibility to incorporate trends and seasonal fluctuations.

A limitation is that the guideline revision was not the only 'interruption'. The study population evolved throughout the study period due to vaccination strategies prioritizing older and high risk individuals. Additionally, the dominant COVID-19 variant changed throughout the study period, which could have affected ICS prescription behaviour. Another possible limitation is that the update of the guideline may not be seen as an isolated intervention at one time point. News in the media about ICS as a possible cure to COVID-19 may have influenced clinicians before the guideline was officially released, and on the other hand, clinicians may only learn about the guideline revision weeks after the update. Due to these additional interruptions, we may have overestimated the instantaneous effect of the update.

Our data quality, while sufficient in sample size, lacked details such as vaccination status and symptom duration, which would be required to strictly measure the adherence to the COVID-19 guideline. Since information on these factors was lacking, we might have overestimated the percentage of patients that satisfied the NHG criteria. Additionally, the advice to prescribe ICS was only to be considered, rather than a 'must follow' guideline, complicating assessment of guideline adherence. We have only data on prescriptions, but no information on whether clinicians considered prescribing, like the guideline recommended. The relatively weak wording in the guideline and

numerous conditions a patient must satisfy, may explain the significant decrease in overall prescription rate after the guideline changed hereto.

Whether medication had been prescribed specifically for COVID-19 or for another disease was unknown for most patients, possibly resulting in an overestimation of prescriptions for COVID-19. By selecting prescriptions occurring within 14 days of a COVID-19 consultation we largely solved this issue.

Implications for research

As of November 28, 2023, the recommendation to prescribe ICS has been withdrawn from the Dutch COVID-19 guideline. The reason is that the benefit of ICS in adults with the omicron variant of COVID-19 and with previous immunity may be smaller and no longer clinically relevant compared to earlier variants of COVID-19.[42] A future study could assess whether this has further decreased the prescription rate.

Our study shows that routine care data can be efficiently used to study behaviour change after guideline changes, which is a time-efficient approach to evaluate an aspect of guideline implementation. Once a guideline has been revised, it is an open question as to how to best communicate these changes to the clinicians. In future studies, these methods can be used to optimize and to measure the effect of different dissemination strategies of guidelines.

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Ethical approval

The Medical Research Ethics Committee Leiden-Den Haag-Delft determined that the Medical Research Involving Human Subject Act (WMO) does not apply to this study and that an official approval by the committee is not required.

Competing interests:

The authors have no conflicts of interest to declare.

Acknowledgements:

None.

Sharing of data

The data that support the findings of this study are available from ELAN but restrictions apply to the availability of these data, which were used under license for the current study, and thus are not publicly available. Data are however available from the authors upon reasonable request and with permission of ELAN.

Table 1. Baseline characteristics of patients that had at least one COVID-19 consultation during the study period.

	Prescribed			Not prescribed
Characteristic	**Before update**, N = 526	**After update**, N = 1,208	**Overall**, N = 1,709	**Overall**, N = 129,773
Sex (male)	193 (36.7%)	441 (36.5%)	627 (36.7%)	59,996 (46.2%)
Age (years)	51.5 (17.2)	48.7 (19.9)	49.6 (19.2)	36.8 (20.4)
Target NHG advice (age >= 65 or age >= 50 with comorbidity*)	225 (42.8%)	475 (39.3%)	689 (40.3%)	17637 (13.6%)
N episodes	2.07 (0.8)	1.50 (0.7)	1.66 (0.8)	1.24 (0.5)
Any of the following comorbidities	320 (60.8%)	718 (59.4%)	1019 (59.6%)	17556 (13.5%)
Asthma	251 (47.7%)	575 (47.6%)	808 (47.3%)	8464 (6.5%)
COPD	42 (8.0%)	109 (9.0%)	151 (8.8%)	1412 (1.1%)
Cardiovascular disease	71 (13.5%)	170 (14.1%)	239 (14.0%)	6837 (5.3%)
Diabetes	4 (0.8%)	7 (0.6%)	11 (0.6%)	402 (0.3%)
Chronic kidney damage	31 (5.9%)	67 (5.5%)	98 (5.7%)	2692 (2.1%)
Liver cirrhosis	11 (2.1%)	13 (1.1%)	23 (1.3%)	674 (0.5%)

Age and N episodes are presented as mean (SD). All other variables are binary and presented as n (%). Age and whether the patient is targeted by the NHG advice is computed at the moment of their first COVID-19 episode. There were 25 patients who were prescribed ICS both before and after guideline update. These are included in both column two and three. * Comorbidities are asthma, COPD, cardiovascular disease, diabetes, chronic kidney damage or liver cirrhosis.

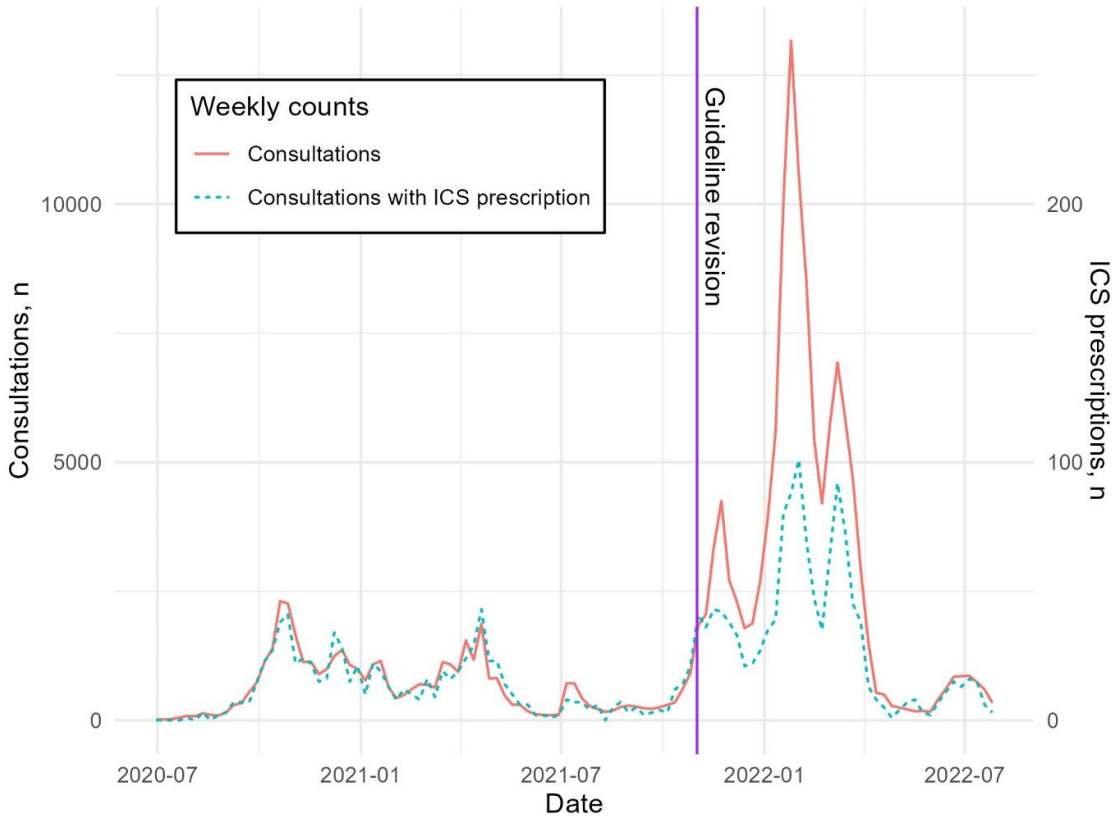

Figure 1 Weekly counts of COVID-19 consultations and COVID-19 consultations with ICS prescriptions. The consultations with ICS prescription follow the scale on the right side of the figure. This scale is chosen such that frequency patterns can be assessed simultaneously. The intervention date was November 2, 2021, which is the day the NHG published their updated guideline with regard to budesonide and is marked with the vertical line.

Table 2. Estimated incidence risk ratio's for quasi-Poisson model for the weekly prescription rate.

Variable	IRR[1]	95% CI[1]	p-value
Weeks after study start	1.00	1.00, 1.01	0.06
After guideline revision (indicator)	0.47	0.32, 0.69	< 0.001
Weeks after guideline revision	1.01	0.99, 1.02	0.31
Q1 (indicator)	0.70	0.58, 0.84	< 0.001
Q2 (indicator)	1.01	0.81, 1.27	0.91
Q3 (indicator)	0.75	0.59, 0.96	0.02

[1] IRR = Incidence Rate Ratio, CI = Confidence Interval.

Weeks after study start represents the trend before guideline revision. After guideline revision (indicator) represents the immediate effect of guideline revision and the row for the weeks after guideline revision represents the trend change with respect to the period before revision. Q1, Q2 and Q3 model seasonal effects in the first, second and third quarter of the year with respect to the fourth quarter.

Autocorrelation has been accounted for by adjusting the confidence interval and p-value using the Newey West method.

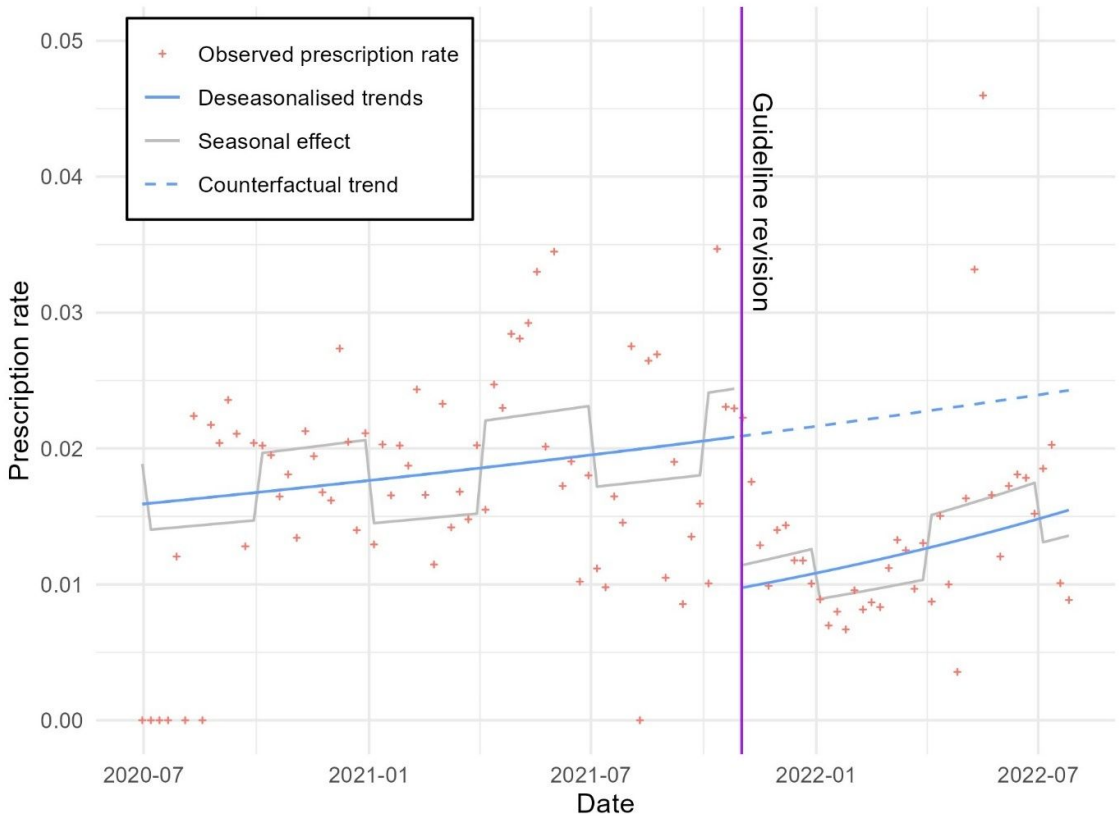

Figure 2 The observed weekly prescription rate (ratio of COVID-19 cases with ICS prescription per COVID-19 consult), along with the trend and seasonal effect. The counterfactual line is formed by continuing the trend estimated from the period before the guideline revision. The vertical line denotes the day of the guideline revision, November 11, 2021.

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