Comparison of drug prescribing before and during the COVID-19 pandemic: A cross-national European study



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# Comparison of Drug Prescribing Before and During the COVID-19 Pandemic – A Cross-national European Study

**Running title:**

**Impact of COVID-19 Pandemic on Drug Prescribing in Europe**

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**Data and Code Availability**

The data and code that support the findings of this study are openly available in “zenodo” at https://doi.org/10.5281/zenodo.5912080.

**Conflicts of Interest**

The authors have no relevant conflicts of interest to declare.

**Ethics approval** and **patient consent** were not needed because only aggregated administrative data were used.

**Authors’ Contributions**

ISK and GWS conceptualized the study with support from BW and MB. GWS and ISK analysed the data. ISK drafted the manuscript with support from GWS, BW, MB, MHH, and FN. CZY, CP and MTP provided data on Catalonia. JS and VK provided data on Czechia. GWS provided data on Germany. KG provided data on Lithuania. EP, CR, SR and MA provided data on Romagna. MB and SM provided data on Scotland. JF and MU provided data on Slovenia. BW provided data on Sweden. All authors participated in critical revision of the manuscript, contributed comments, and approved the final version.

**Supplementary Material**

The Supplementary Material for this article can be found online at [to be determined].

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## Abstract

### Purpose

The COVID-19 pandemic had an impact on health care, with disruption to routine clinical care. Our aim was to describe changes in prescription drugs dispensing in the primary and outpatient sectors during the first year of the pandemic across Europe.

### Methods

We used routine administrative data on dispensed medicines in eight European countries (five whole countries, three represented by one region each) from January 2017 to March 2021 to compare the first year of the COVID-19 pandemic with the preceding three years.

### Results

In the 10 therapeutic subgroups with the highest dispensed volumes across all countries/regions the relative changes between the COVID-19 period and the year before were mostly of a magnitude similar to changes between previous periods. However, for drugs for obstructive airway diseases the changes in the COVID-19 period were stronger in several countries/regions.

In all countries/regions a decrease in dispensed DDDs of antibiotics for systemic use (from –39.4% in Romagna to –14.2% in Scotland) and nasal preparations (from –34.4% in Lithuania to –5.7% in Sweden) was observed.

We observed a stockpiling effect in the total market in March 2020 in six countries/regions. In Czechia the observed increase was not significant and in Slovenia volumes increased only after the end of the first lockdown.

We found an increase in average therapeutic quantity per pack dispensed, which, however, exceeded 5% only in Slovenia, Germany, and Czechia.

### Conclusions

The findings from this first European cross-national comparison show a substantial decrease in dispensed volumes of antibiotics for systemic use in all countries/regions. The results also indicate that the provision of medicines for common chronic conditions was mostly resilient to challenges faced during the pandemic. However, there were notable differences between the countries/regions for some therapeutic areas.



### Keywords

COVID-19, pandemic, drug utilization, pharmacoepidemiology, cross-national comparison, DDD volume, stockpiling


### Key Points

- Dispensed volumes of systemic antibiotics and nasal preparations decreased in all countries/regions.
- Provision of medicines for common chronic conditions was mostly resilient to challenges faced during the COVID-19 pandemic.

- Stockpiling of pharmaceuticals was observed typically in March 2020, except for Slovenia, where increases of DDD volume were observed only two months later.

**The Plain Language Summary** (PLS)

The COVID-19 pandemic had an impact on many aspects of life including health care. We assumed that also drug prescribing would be affected. Our aim was to describe changes in prescription drug dispensing in the outpatient sector during the first year of the pandemic across Europe. We used large data sets on dispensed volumes of medicines and their pack sizes in eight European countries (five whole countries and three represented by one region each), comparing the first year of the COVID-19 pandemic and the preceding three years. In all countries/regions we observed a substantial decrease in dispensed volumes of antibiotics for systemic use (i.e. usually oral antibiotics) and nasal preparations. In March 2020 we observed an increase in dispensed volume of medicines in all countries/regions but Slovenia, where this effect occurred only after the end of the lockdown connected to the first wave of the pandemic. Increases in average pack size dispensed were rather mild and exceeded 5% only in three of the countries/regions. Although the first year of the pandemic brought substantial changes in dispensed volumes of medicines, it is reassuring that medicines for treating common chronic conditions were usually little affected.

# Introduction

The first cases of COVID-19 were confirmed in Europe at the end of January 2020. In March 2020, the World Health Organization (WHO) declared a COVID-19 pandemic and countries began to take measures to mitigate the spread of the pandemic. Many European countries introduced strict measures during March 2020, including physical distancing, wearing face masks, and limiting possibilities of social contacts, however, the nature of these measures varied substantially between and within countries.[1]

The COVID-19 pandemic has affected peoples' lives and behaviour in many aspects and has also had a significant impact on health care.[2,3] Many planned health care examinations and procedures have been cancelled or postponed, as clinical staff were re-allocated to health care services related to COVID-19 and patients tried to limit their visits to physicians to avoid the risk of contracting the infection in healthcare facilities. In December 2020, the EU-funded European Network to Advance Best practices & technoLogy on medication adherencE (ENABLE) COST Action conducted a survey in 39 European countries to assess barriers and facilitators for patients accessing their chronic medication during the pandemic.[4,5] The survey indicated significant disruption of chronic disease services, especially in countries with a greater number of COVID-19 cases per 100,000 inhabitants, and a large variation between countries in measures taken to ensure adequate drug management for these patients.

We hypothesized that, like other areas of health care, the pandemic would affect also the patterns of drug prescribing and dispensing. Given that there were substantial differences between countries in measures to maintain medicines management during the pandemic, cross-national comparisons of drug utilization patterns may add value as a tool to identify areas for improvement. The aim of this paper was to characterize and compare changes that took place in prescription drugs dispensing in primary care and the outpatient sector in several European countries or regions during the first year of the pandemic.

# Methods

## Study design and data

We conducted a retrospective observational cross-national comparative study. Participating countries and regions were Czechia, Germany, Romagna (Italy), Lithuania, Slovenia, Catalonia (Spain), Sweden, and Scotland (United Kingdom). For each country/region, we used dispensing data[6] from January 2017 to March 2021. Data covered all dispensed prescription medicines of the countries/regions and included the codes of the Anatomical-

Therapeutic-Chemical classification (ATC) and corresponding numbers of dispensed defined daily doses (DDDs) and packs, both aggregated by month. We used the ATC classification of 2021, as published by the World Health Organization (WHO),[7] for the whole study period. The details on data sources and populations covered are in Table S1 in the Supplement.

**Data analysis**

To describe changes in dispensed volumes of pharmaceuticals we used percentages. For the analysis of changes in pack sizes we employed index decomposition methods from economics.[8,9]

To compare the drug consumption before the COVID-19 pandemic and during the COVID-19 pandemic, we used only data for four successive twelve-months periods from March 2017 to February 2021. We compared the drug consumption in the first twelve-month period with COVID-19 with the three preceding twelve-month periods. To assess total market development on a monthly scale, we used monthly data for the whole period from January 2017 to March 2021. Data analysis was performed using R 4.1.0.[10]

*Definitions used*

DDD/TID – number of dispensed DDDs[7] per Thousand Inhabitants per Day

Therapeutic quantity per pack – number of defined daily doses (DDDs) per pack; also referred to as *pack size*

Period 1 – March 2017 to February 2018
Period 2 – March 2018 to February 2019
Period 3 – March 2019 to February 2020 (pre-COVID period)
Period 4 –March 2020 to February 2021 (COVID period)

*Choice of therapeutic drug subgroups for analysis*

The first step was an analysis of therapeutic subgroups (ATC level 2).[7] We adopted two complementary approaches: firstly, we analysed the therapeutic subgroups with the highest DDD volume; secondly, we analysed the therapeutic subgroups with the most marked changes in DDD volume when comparing the COVID period with preceding periods.

For the purpose of comparing periods and countries/regions, we expressed the volume of the dispensed DDDs in each period as DDD/TID. We used the following equation:

$$v_p = \frac{\sum_{m=1}^{12} u_{m,p}}{d_p\, n_p} \cdot 1000$$

$v_p$ … dispensed volume in period $p$ [DDD/TID]

$u_{m,p}$ … dispensed volume in month $m$ of period $p$ [DDD]

$d_p$ … number of days in period $p$

$n_p$ … size of population covered in period $p$ (see Table S1 for details)

To calculate relative changes in dispensed DDD/TID between consecutive twelve-month periods we used the following equation:

$$\Delta_p = \frac{v_p}{v_{p-1}} - 1$$

$\Delta_p$ … relative change between periods $p$ and $p$–1

### *Changes in dispensed DDDs – ATC groups with the highest dispensed volume*

In order to identify changes in the COVID period compared to pre-COVID times, we first focused on the ten therapeutic subgroups with the highest dispensed DDD/TID volume. (For details of the selection procedure see Figure S1 in the Supplement.) For these ten groups and for each country separately, we then investigated changes in dispensed DDDs for the COVID period compared to the previous period. To guard against mistaking longer-term trends for COVID-related changes, we also checked changes in earlier periods.

### *Changes in dispensed DDDs – ATC groups with the most marked changes*

Additionally, for each country, we determined the ten therapeutic subgroups with the most marked changes. We excluded all therapeutic subgroups where dispensed DDD/TID in the pre-COVID period were less than 0.1, because infrequently dispensed pharmaceuticals are more prone to high fluctuations which could be unrelated to COVID. (For further details of the selection procedure see Figure S2 in the Supplement.) For each country and its ten selected therapeutic subgroups, we identified the main volume contributors on ATC level 4 (chemical subgroups) and described their changes in volume.

### Changes in dispensed DDDs – total market development on a monthly scale

To see the development of the total market during the COVID period in finer temporal resolution and to compare it to previous years, we used for each country the monthly volumes (in DDD/TID) of all pharmaceuticals. Because of seasonality and autocorrelation in the data we used ARIMA models to assess the impact of the pandemic. The first step was to estimate the noise in the time series using only data from January 2017 to February 2020. In step two we modelled the whole time series (January 2017 to March 2021), adding two events: one with immediate onset and permanent duration to model lasting influence of the pandemic, the other with immediate onset and short duration to capture the large fluctuations in the first three months of the pandemic. We used the Ljung-Box test on the residuals to test for the presence of remaining autocorrelation. Stationarity and seasonal stationarity were tested with the Kwiatkowski-Phillips-Schmidt-Shin test and the Hylleberg-Engle-Granger-Yoo test respectively. Statistical significance of coefficients in the models was tested using the z-test. Tests were performed at the 0.05 significance level.

### Changes in dispensed therapeutic quantity per pack

The average therapeutic quantity per pack is calculated as the ratio of number of dispensed DDDs and number of dispensed packs. Changes in this average pack size are influenced both by changes in the number of units or the dosage strengths of the units dispensed and by changes in the market mix, because some therapeutic areas typically use bigger pack sizes than others. For instance, the pack size of pharmaceuticals typically prescribed for antidiabetic treatment is greater than in antibiotic therapy. Thus any reduction in antibiotic dispensing would lead to an increase of average pack size reported for the total market even if average pack size dispensed within antibiotic therapy and also average pack size within diabetic therapy remained unchanged. In order to account for this fact we employed a concept of index theory from economics.[8,9] We explain the relative change in average pack size $\Delta u$ as a combined effect of shifts in average dispensed pack sizes $\Delta v$ within the therapeutic subgroups and of structural changes in the market $\Delta s$, i. e., shifts in the market shares of those subgroups, where $\Delta u = \Delta v \cdot \Delta s$. (See Supplement, section Changes in therapeutic quantity per pack, for more details.)

In order to concentrate on longer-lasting effects, we compared pack sizes dispensed during the second half of the COVID period (September 2020 to February 2021), with the values from the corresponding period one year before (September 2019 to February 2020), just before the start of the pandemic. To assess possible longer-term trends, we also obtained the corresponding values for the same months in 2017/18 and 2018/19. The analysis was performed on ATC level 2. In order to check stability with respect to the choice of ATC level, we also performed the calculations on ATC level 4.

# Results

## Changes in dispensed DDDs

### *Changes in dispensed DDDs between the pre-COVID period and the COVID period– ATC groups with the highest dispensed volume in the pre-COVID period*

The ten therapeutic groups with the highest dispensed volumes in the pre-COVID period (measured by DDD/TID) across all countries/regions were drugs for acid related disorders (A02), antidiabetics (A10), antithrombotics (B01), antianemic preparations (B03), beta-blockers (C07), calcium channel blockers (C08), ACE inhibitors/ARBs (C09), lipid modifying agents (C10), psychoanaleptics (N06) and drugs for asthma/COPD (R03). The relative changes between the pre-COVID period and the COVID period in all these therapeutic subgroups (apart from antiasthmatics) were mostly of a magnitude similar to the changes between previous periods (Figure 1). For antiasthmatics/COPD-drugs, more fluctuating patterns were observed. In Catalonia, Romagna, and Slovenia the dispensed DDD volume decreased, whereas in Scotland and Sweden we observed a slight increase and in the rest of the countries/regions the volumes stayed approximately on the same level (Figure 1). For more detail see Supplement, Table S3. For a comparison of first and second half year of the pandemic see Supplement, Figures S3 and S4.

### *Changes in dispensed DDDs between the pre-COVID period and the COVID period – ATC groups with the most marked changes compared to the pre-COVID period*

The ten therapeutic subgroups with the greatest relative changes (i.e. $|\Delta_p|$) between the pre-COVID period and the COVID period for each participating country are shown in Figure 2. The main contributors on chemical (ATC $4^{th}$ level) subgroups which together cover at least 2/3 of the DDD volume for the therapeutic (ATC $2^{nd}$ level) subgroups are shown in the Supplement in Tables S4–S11.

In all countries/regions, systemic antibiotics (J01) were among the top ten therapeutic subgroups, and in all countries/regions their volume decreased. All subgroups of systemic antibiotics decreased in the COVID period compared to the pre-COVID period, except for tetracyclines in Lithuania with 0.9% increase of DDD/TID and third generation cephalosporins (J01DD) in Czechia, where DDD/TID increased by 52%, however it accounted for only 0.7% of the J01 DDD volume in the pre-COVID period.

Also nasal preparations (R01) belonged to the top ten therapeutic subgroups with the greatest changes in volume in almost all countries/regions. The only exception was Romagna. In all countries/regions including Romagna the volumes decreased.

The third most frequently appearing group in the list of groups with most marked changes were the antimycotics for systemic use (J02). It reached the top ten in five countries/regions (Catalonia, Romagna, Lithuania, Scotland, and Slovenia). In all cases the volumes decreased during the COVID period. Volume also decreased in Sweden, Germany and Czechia, although in Germany and Czechia the decrease was only approximately 2% and did not exceed changes seen in previous periods. Overall, there was a high variability in the top ten therapeutic subgroups with most marked changes in volume among countries/regions.

For a comparison of first and second half year of the pandemic see Supplement, Figures S5 and S6.

### *Changes in dispensed DDDs – total market development on a monthly scale*

In Germany, Lithuania, Scotland, and Sweden, we observed a marked increase in March 2020 followed by a decrease which in April and/or May 2020 went below the levels in previous years. In Romagna and Catalonia this pattern was weaker. In Czechia there were hints of a similar pattern too, however in this country a strong quarterly rhythm could be observed in previous years. In Slovenia, unlike in other countries/regions, there was a decrease in March and April 2020, followed by a peak in May 2020, followed by a return to the level of 2019 in July (Fig. 3). In all countries/regions but in Czechia taking into account the events with immediate effect and short duration (see Methods) significantly improved the fit of the model, whereas the durable impact of pandemic was significant only in Catalonia and Romagna. For more detail see Supplement, Table S12 and Figures S7 and S8.

## Changes in average number of DDDs per pack

### *Analysis for therapeutic (ATC 2nd level) subgroups*

In the six months immediately preceding the pandemic, the increases in the average therapeutic quantity per pack dispensed were between +0.5 and +3.1% in all the countries/regions, with the exception of Romagna at +4.3% (Table 1). During the pandemic, the increases were below +2.5% in four countries/regions. The lowest value of these, 0.0% (no increase), was recorded for Lithuania, where a shift towards smaller pack sizes (–1.6%) was offset by a positive structural shift of the same magnitude.

The other four countries/regions showed increases of between +4.7 and +7.7%. Most of these increases were due to shifts to higher numbers of DDDs per pack within the therapeutic subgroups (Czechia +4.3%, Romagna +3.1%, Slovenia +6.0%), whereas in Germany such shifts accounted for only +1.9%. Here the structural changes in the market contributed +4.1% to the total increase in average pack size.

### *Analysis for chemical (ATC 4th level) subgroups*

Results were similar to those observed for therapeutic subgroups. In the majority of countries, shifts between the chemical subgroups were slightly stronger than between therapeutic subgroups, except for Slovenia, where the shifts towards bigger packs within subgroups were even stronger than at a higher ATC-level. (See Table S13 in the Supplement for details.)

## Discussion

In this cross-national comparative study including eight European countries/regions we assessed utilization patterns of all prescription drugs before and during the first year of the COVID-19 pandemic. We found limited impact of the pandemic on the most commonly used prescription drugs in all countries/regions, but there were some differences between countries/regions in trends of certain pharmaceuticals.

The small changes observed in the ten groups with the highest dispensed volume suggest that drug usage for the most common chronic diseases was little affected by the pandemic. With few exceptions, the change in volume of these drugs followed trends seen in previous years. This holds particularly for the cardiovascular diseases and diabetes drugs, which is compatible with the findings of Carr et al.[11] It is positive that we found no substantial decrease in utilization of these drugs in any country. However, it is important to acknowledge that there may still be problems of underuse of these agents. Diabetes and hypertension have both been found to be strong independent risk factors for severe COVID-19,[12] and there is an increasing number of studies showing the beneficial effects of treatment for diabetes and cardiovascular diseases in the prognosis and outcome of COVID-19.[13–16]

A partial exception to these trends are drugs used in the treatment of COPD and asthma. Several countries/regions experienced a decrease in the use of these medicines, which might be connected to less exposure to exacerbating factors due to lockdowns and similar measures. Notably, Sweden as the only country without any formal lockdown during the reporting period showed a small increase in the dispensed volume of these drugs.

There have been discussions about the impact of the pandemic on mental health. Although there is some evidence for increased loneliness, anxiety, stress, and depression,[17–20] we found no strong reflection of this on the dispensed volumes of either psycholeptic or psychoanaleptic drugs (see Figure S9 in the Supplement).

In all participating countries/regions, we noted a decrease in dispensed volume of antibiotics and nasal preparations. The observed decrease in dispensed volume of antibiotics was in line with other studies.[21–24] We assume that lower need of these pharmaceuticals in the COVID period might be a consequence of lockdown and other forms of social distancing, resulting in fewer occasions for transmitting infections.

In general, the largest decreases were observed in therapeutic subgroups used predominantly for non-life-threatening conditions. This suggests a rational approach by patients and/or physicians to the minimisation of contacts during the pandemic: postponing treatment of less serious conditions while maintaining vital treatment regimes.

A number of countries/regions showed a marked increase of the overall dispensed volume right at the beginning of the pandemic, followed by a notable decrease. We surmise that this is a case of stockpiling,[25] as was also seen for a number of other (non-pharmaceutical) goods.[26,27] In times of uncertainty over the imminent future, drugs for which the need was known or possible to plan were prescribed and redeemed in bigger quantities than usual, and were consequently used over subsequent periods. Again, this is compatible with rational behaviour in two respects: firstly, this safe-guarded the individual against shortages, and secondly, it obviated the need for visits to physicians' offices with the risk of catching a COVID infection.

Interestingly, Slovenia showed the opposite development. There was a substantial decrease during March and April 2020, followed by a peak in May. Slovenian patients apparently also avoided visits to physicians for receiving renewal prescriptions, but trusted the system to guarantee continued supply. After the lockdown terminated, depleted stocks were refilled.

For the beginning of the second wave of the COVID-19 pandemic at the break of summer and autumn 2020 we did not observe stockpiling patterns, which suggests a calmer approach by patients based on the experience gained during the first wave.

**Strengths and limitations**

To the best of our knowledge, this is the first cross-national study of the trends of dispensed prescriptions through the pandemic. It uses large administrative databases with complete data on all dispensed prescription medicines in the participating countries resp. regions. Thus, it allows identification of both common trends and differences between countries/regions.

The major limitation is that we investigated only medicines dispensed in ambulatory care. The data included both dispensed prescriptions from general practice and secondary care specialists, but there was no inpatient utilization data assessed, and this may have varied between countries/regions. Secondly, we had to restrict the cross-national comparison to rates of change. A comparison of absolute values of dispensed volumes was not possible due to different national rules for reimbursement in some therapeutic areas. Thirdly, we used aggregated data and could, consequently, not assess if any changes in prevalence, incidence or discontinuation had taken place for the specific drug groups. For this, further research and more detailed analysis on the patient level would be needed. Fourthly, we cannot make causal attribution of changes in the COVID period to the pandemic because we cannot exclude concomitant factors. Finally, it is important to acknowledge that it was not possible to assess the impact of lock-down and other measures given that these varied substantially in nature and across time, both between and within countries/regions.

## Conclusions

In this study we assessed utilization patterns of all prescription medicines before and during the first year of the COVID-19 pandemic in eight European countries/regions. We have identified a number of patterns common to all the countries/regions. In particular, we observed a substantial decrease in dispensed volumes of antibiotics for systemic use. It is reassuring that medicines from therapeutic subgroups used for treating common chronic conditions were usually little affected, which suggests that there was no under-supply of these medicines. However, there were also notable differences between the countries/regions for some therapeutic areas, which may reflect different approaches by physicians and/or patients to the pandemic situation.

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Table 1: Relative change (%) in average therapeutic quantity per pack ($\Delta u$) broken down to changes of average therapeutic quantity per pack within therapeutic subgroups ($\Delta v$) and change of market shares of the therapeutic subgroups ($\Delta s$) for eight European countries/regions, September to February in the years 2017 to 2021; therapeutic subgroups at ATC level 2

| Base period: | 9/2017 to 2/2018 | | | 9/2018 to 2/2019 | | | 9/2019 to 2/2020 | | |
|---|---|---|---|---|---|---|---|---|---|
| Period under review: | 9/2018 to 2/2019 | | | 9/2019 to 2/2020 | | | 9/2020 to 2/2021 | | |
| Country | $\Delta v$ | $\Delta s$ | $\Delta u$ | $\Delta v$ | $\Delta s$ | $\Delta u$ | $\Delta v$ | $\Delta s$ | $\Delta u$ |
| Catalonia | 1.013 | 1.001 | 1.014 | 1.006 | 0.998 | 1.004 | 1.014 | 1.010 | 1.024 |
| Czechia | 1.015 | 0.996 | 1.011 | 1.021 | 1.005 | 1.027 | 1.043 | 1.014 | 1.058 |
| Germany | 1.004 | 1.012 | 1.016 | 1.006 | 1.008 | 1.014 | 1.019 | 1.041 | 1.060 |
| Lithuania | 1.001 | 1.009 | 1.010 | 1.012 | 0.999 | 1.011 | 0.984 | 1.016 | 1.000 |
| Romagna | 1.003 | 1.001 | 1.005 | 1.028 | 1.014 | 1.043 | 1.031 | 1.016 | 1.047 |
| Scotland | 1.005 | 1.008 | 1.013 | 0.997 | 1.008 | 1.004 | 1.009 | 1.013 | 1.022 |
| Slovenia | 1.019 | 0.999 | 1.018 | 1.025 | 1.006 | 1.031 | 1.060 | 1.016 | 1.077 |
| Sweden | 0.998 | 1.008 | 1.006 | 1.010 | 1.003 | 1.012 | 1.008 | 1.009 | 1.017 |

Note: $\Delta v$: relative change in average therapeutic quantity per pack within therapeutic subgroups; $\Delta s$: structural changes in the market; $\Delta u$: combined total effect.

Figure 1: Top ten therapeutic subgroups with highest dispensed volume (in pre-COVID period) across eight European countries/regions: relative change of DDD/TID between four 12-month periods March 2017 to February 2021

{See separate file Figure_1.png}

Legend for Figure 1:

Periods:
Period 1: March 2017 – February 2018
Period 2: March 2018 – February 2019
Pre-COVID period: March 2019 – February 2020
COVID period: March 2020 – February 2021

Country codes:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAT | Catalonia | CZE | Czechia | DEU | Germany | LTU | Lithuania |
| RMN | Romagna | SCO | Scotland | SVN | Slovenia | SWE | Sweden |

Therapeutic subgroups:

| | | | |
|---|---|---|---|
| A02 | Drugs for acid related disorders | C08 | Calcium channel blockers |
| A10 | Drugs used in diabetes | C09 | Agents acting on the renin-angiotensin system |
| B01 | Antithrombotic agents | C10 | Lipid modifying agents |
| B03 | Antianemic preparations | N06 | Psychoanaleptics |
| C07 | Beta blocking agents | R03 | Drugs for obstructive airway diseases |

Figure 2: Top ten therapeutic subgroups with most marked relative change in DDD per 1000 inhabitants per day (DDD/TID) volume (in the COVID period relative to the pre-COVID period) for eight European countries/regions between four 12-month periods within March 2017 to February 2021
(Only changes that were larger for the COVID period than for any period before the onset of COVID-19 are shown. Therapeutic subgroups with DDD/TID ≤ 0.1 were excluded.)

{See separate file Figure_2.png}

Legend for Figure 2:

Periods:
Period 1: March 2017 – February 2018
Period 2: March 2018 – February 2019
Pre-COVID period: March 2019 – February 2020
COVID period: March 2020 – February 2021

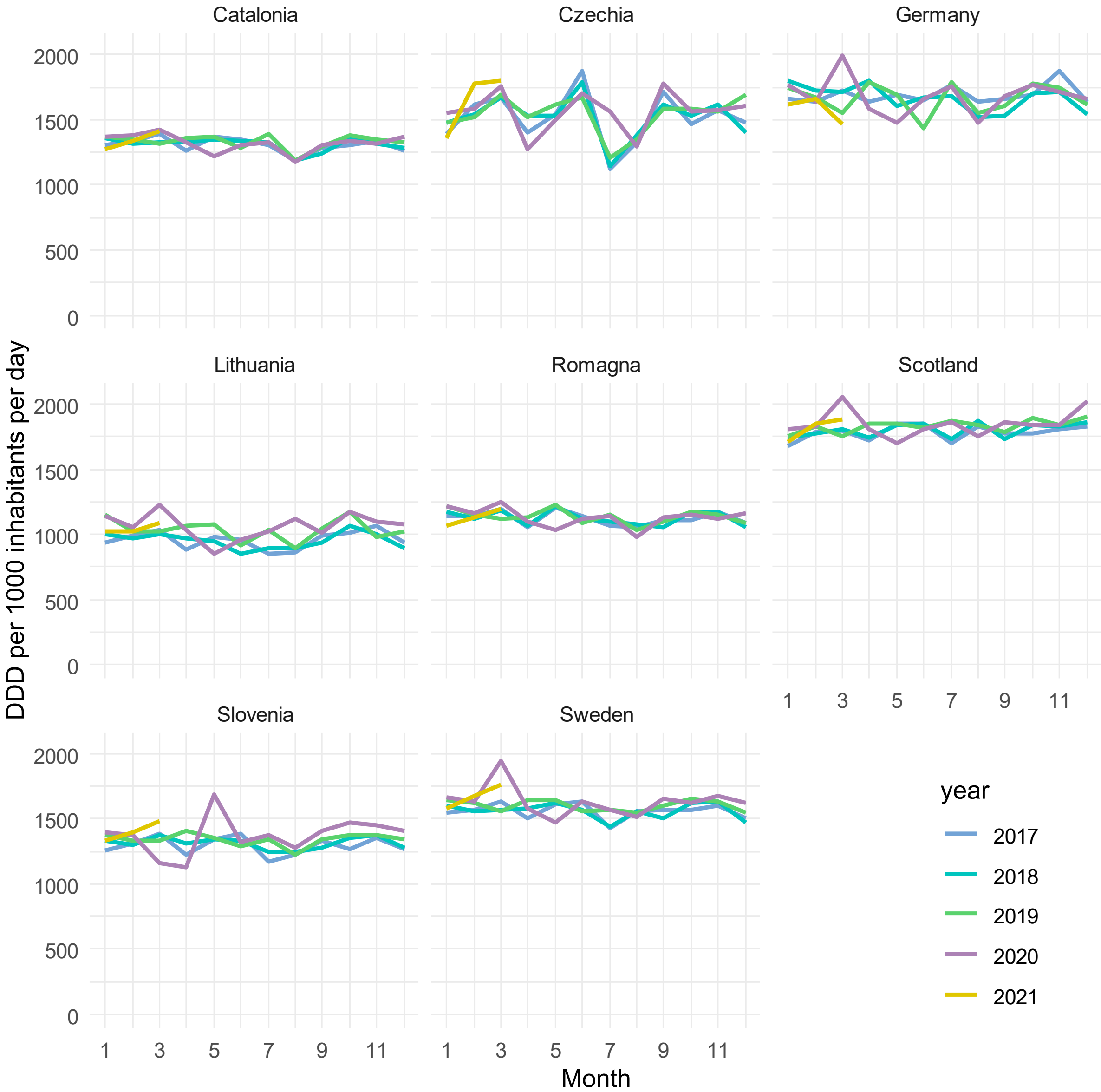
Country codes:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAT | Catalonia | CZE | Czechia | DEU | Germany | LTU | Lithuania |
| RMN | Romagna | SCO | Scotland | SVN | Slovenia | SWE | Sweden |

Therapeutic subgroups

| | | | |
|---|---|---|---|
| A01 | Stomatological preparations | H02 | Corticosteroids for systemic use |
| A02 | Drugs for acid related disorders | J01 | Antibacterials for systemic use |
| A03 | Drugs for functional gastrointestinal disorders | J02 | Antimycotics for systemic use |
| A08 | Antiobesity preparations, excl. diet products | J04 | Antimycobacterials |
| A11 | Vitamins | J05 | Antivirals for systemic use |
| A12 | Mineral supplements | J06 | Immune sera and immunoglobulins |
| B02 | Antihemorrhagics | L02 | Endocrine therapy |
| B03 | Antianemic preparations | M01 | Antiinflammatory and antirheumatic products |
| C02 | Antihypertensives | M02 | Topical products for joint and muscular pain |
| C04 | Peripheral vasodilators | M03 | Muscle relaxants |
| D01 | Antifungals for dermatological use | N02 | Analgesics |
| D04 | Antipruritics, incl. antihistamines, anesthetics, etc. | P01 | Antiprotozoals |
| D05 | Antipsoriatics | P02 | Anthelmintics |
| D07 | Corticosteroids, dermatological preparations | P03 | Ectoparasiticides, incl. scabicides, insecticides and repellents |
| D08 | Antiseptics and disinfectants | R01 | Nasal preparations |
| D10 | Anti-acne preparations | R02 | Throat preparations |
| D11 | Other dermatological preparations | R03 | Drugs for obstructive airway diseases |
| G01 | Gynecological antiinfectives and antiseptics | R05 | Cough and cold preparations |
| G02 | Other gynecologicals | R06 | Antihistamines for systemic use |
| G03 | Sex hormones and modulators of the genital system | S02 | Otologicals |
| H01 | Pituitary and hypothalamic hormones and analogues | | |

Figure 3: Total market development in DDD per 1000 inhabitants per day (DDD/TID) on a monthly scale for eight European countries/regions, January 2017 to March 2021



Supplementary material for

# Comparison of Drug Prescribing Before and During the COVID-19 Pandemic – A Cross-national European Study

**Pharmacoepidemiology and Drug Safety**

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This supplement contains details on data sources, calculation of therapeutic quantities in packs, dispensed DDD per 1000 inhabitants per day (DDD/TID), and their relative changes in the periods before and during the COVID-19 pandemic. It also contains details of the ARIMA time series models.

**Table S1:** Data sources

| Region | Source for dispensed volumes of medicines | Population size in years 2017 to 2020 | | | | Source for population size |
|---|---|---|---|---|---|---|
| | | 2017 | 2018 | 2019 | 2020 | |
| Catalonia | Receptes facturades al Servei Català de la Salut. Health Department. Generalitat de Catalunya. | 7 488 302 | 7 518 913 | 7 570 452 | 7 653 845 | Registre central de població acreditada del Servei Català de la Salut (RCA). Health Department. Generalitat de Catalunya |
| Czechia | State Institute for Drug Control – DIS-13 Reporting supplies of distributed human medicinal products | 10 589 526 | 10 626 430 | 10 669 324 | 10 701 777 | Czech Statistical Office (https://www.czso.cz/) |
| Germany | GAmSi database at AOK Research Institute (WIdO) | 72 258 037 | 72 802 100 | 73 009 237 | 73 357 862 | Bundesministerium für Gesundheit (https://www.bundesgesundheitsministerium.de/themen/krankenversicherung/zahlen-und-fakten-zur-krankenversicherung/mitglieder-und-versicherte.html) |
| Lithuania | State Medicines Control Agency | 2 824 030 | 2 801 501 | 2 792 209 | 2 796 025 | Statistics Lithuania (https://www.stat.gov.lt/#) |
| Romagna | Prescribing Information System for Approved Drugs by the National Health Service" | 1 117 581 | 1 118 683 | 1 120 905 | 1 120 074 | ISTAT (http://dati.istat.it/) |
| Scotland | NHS Scotland Prescribing Information System (PIS) | 5 424 800 | 5 438 100 | 5 463 300 | 5 465 000 | National Records of Scotland (https://nrscotland.gov.uk) |
| Slovenia | Database at Health Insurance Institute of Slovenia | 2 066 161 | 2 070 050 | 2 089 310 | 2 100 126 | Statistical Office of Republic of Slovenia (https://www.stat.si/StatWeb/en) |
| Sweden | Prescription dispensing data from the Swedish E-health Agency | 9 995 153 | 10 120 242 | 10 230 185 | 10 327 589 | Swedish population Statistics (https://www.scb.se) |

Note: Population sizes were determined to 1st July of the respective years with the following exceptions: Catalonia – 31st December, Czechia – 30th June, Romagna and Sweden – 1st January. Population sizes used for calculations in each period are those for the year in which the period started.

Figure S1: Selection procedure for the ten therapeutic subgroups with the highest volume across countries/regions

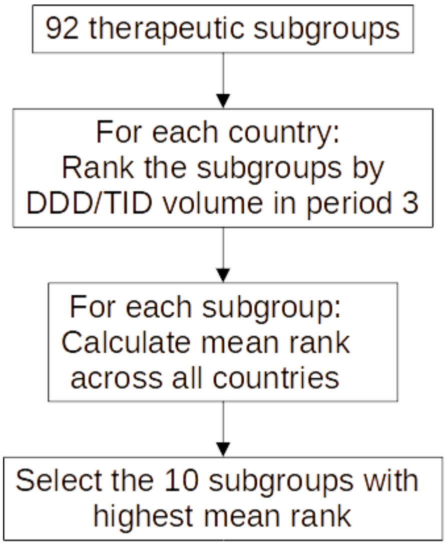
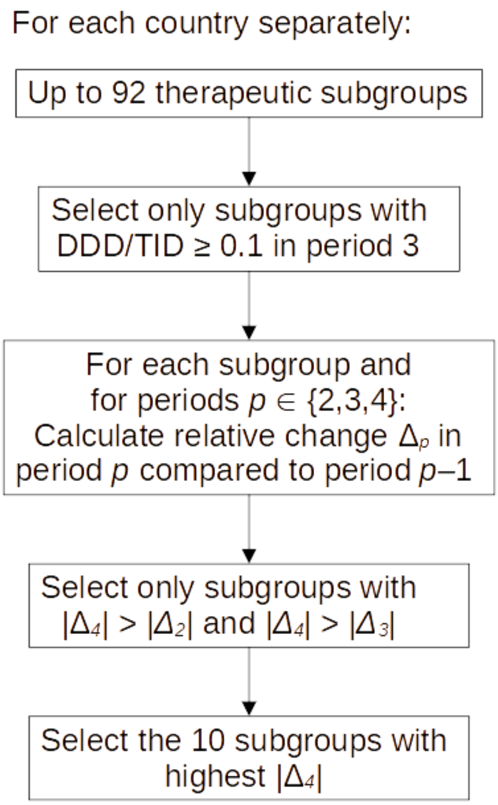



Figure S2: Selection procedure for the ten therapeutic subgroups with the largest changes per country



### Changes in therapeutic quantity per pack

Changes in the average therapeutic quantity per pack (DDDs per pack) are influenced both by changes in the number of units or the dosage strength of the units in dispensed packs and by structural changes in the market.

Let us divide the whole market into the therapeutic subgroups indexed by $i$. Let $d_i^0$ be the DDD volume of therapeutic subgroup $i$ in the base period and $d_i^1$ the DDD volume in the period of interest and similarly for the number of packs $p_i^0$ and $p_i^1$. Then $u_i^0 = \frac{d_i^0}{p_i^0}$ and $u_i^1 = \frac{d_i^1}{p_i^1}$ are the average number of DDDs per pack in therapeutic subgroup $i$ in the two periods. The corresponding values for the whole market will be denoted without the subscript ($d^0$, $d^1$and so forth).

We define the relative change in overall DDD volume in the whole market as $\Delta d$, the relative overall change in number of packs as $\Delta p$, and the relative overall change in average number of DDDs per pack as $\Delta u$.

$$\Delta d = \frac{\sum_i d_i^1}{\sum_i d_i^0} = \frac{d^1}{d^0}$$

$$\Delta p = \frac{\sum_i p_i^1}{\sum_i p_i^0} = \frac{p^1}{p^0}$$

$$\Delta u = \frac{\Delta d}{\Delta p}$$

By substituting for $d_i^0$ and $d_i^1$ and expanding the ratio by $\frac{\sum_i u_i^1 p_i^0}{\sum_i u_i^1 p_i^0}$ we get

$$\Delta d = \frac{\sum_i u_i^1 p_i^1}{\sum_i u_i^0 p_i^0} = \frac{\sum_i u_i^1 p_i^0}{\sum_i u_i^0 p_i^0} \cdot \frac{\sum_i u_i^1 p_i^1}{\sum_i u_i^1 p_i^0}$$

The first factor on the right side of the equation corresponds to the relative change of overall DDD volume under the assumption that therapeutic quantities per pack changed as they did in reality, but the number of packs had stayed fixed at the base period level. Thus this term expresses the effect of changes in the average number of DDDs per pack prescribed, cleaned of any changes in the numbers of packs, as introduced in the first paragraph of this section. We refer to this term as $\Delta v$.

Conversely, the second factor on the right side of the equation represents the relative change of overall DDD volume not attributable to changes in numbers of DDDs per pack (keeping DDDs per pack constant), but to changes in the numbers of packs. We will denote this factor with $\Delta q$.

Thus we get:

$$\Delta v = \frac{\sum_i u_i^1 p_i^0}{\sum_i u_i^0 p_i^0}$$

$$\Delta q = \frac{\sum_i u_i^1 p_i^1}{\sum_i u_i^1 p_i^0}$$

$$\boldsymbol{\Delta d = \Delta v \cdot \Delta q}$$

We analyze $\Delta q$ further by expanding it with $p^1/p^0$ and regrouping:

$$\boldsymbol{\Delta q = \frac{\sum_i u_i^1 p_i^1}{\sum_i u_i^1 p_i^0} = \frac{p^1}{p^0} \cdot \frac{\left(\sum_i u_i^1 p_i^1\right) \cdot p^0}{\left(\sum_i u_i^1 p_i^1\right) \cdot p^1} = \frac{p^1}{p^0} \cdot \frac{\frac{\sum_i u_i^1 p_i^1}{p^1}}{\frac{\sum_i u_i^1 p_i^1}{p^0}} = \Delta p \cdot \frac{\sum_i u_i^1 \frac{p_i^1}{p^1}}{\sum_i u_i^1 \frac{p_i^0}{p^0}}}$$

The ratios $\boldsymbol{p_i^0/p^0}$ and $\boldsymbol{p_i^1/p^1}$ represent the market share of therapeutic subgroup $i$ in the total market measured by number of packs.

Hence, the factor $\frac{\sum_i u_i^1 \frac{p_i^1}{p^1}}{\sum_i u_i^1 \frac{p_i^0}{p^0}}$ is clean of changes in the overall number of packs. It corresponds to the structural shifts within the market while keeping pack sizes fixed. Thus it expresses the effect that changing market shares for each therapeutic subgroup have on $\Delta q$. We will denote this factor as $\Delta s$.

From $\boldsymbol{\Delta q = \Delta p \cdot \Delta s}$ we have

$$\boldsymbol{\Delta d = \Delta p \cdot \Delta v \cdot \Delta s}$$

and finally

$$\Delta u = \frac{\Delta d}{\Delta p} = \Delta v \cdot \Delta s$$

We can thus explain the change in average therapeutic quantity per pack $\Delta u$ as a combined effect of changes in the dispensed therapeutic quantities per pack within the individual therapeutic subgroups ($\Delta v$) and of structural shifts in the market shares of those subgroups ($\Delta s$).

**Table S2**: Age and sex distribution of populations covered

| Country | CATALONIA | | CZECHIA | | GERMANY | |
|---|---|---|---|---|---|---|
| Age (years) | % | % female | % | % female | % | % female |
| 0-9 | 9.1 | 48.6 | 10.5 | 48.8 | 8.8 | 48.7 |
| 10-19 | 11.0 | 48.2 | 10.1 | 48.7 | 8.9 | 48.5 |
| 20-29 | 11.0 | 48.4 | 10.3 | 48.5 | 11.6 | 48.1 |
| 30-39 | 12.6 | 50.2 | 13.8 | 48.4 | 13.5 | 49.1 |
| 40-49 | 16.6 | 49.5 | 16.6 | 48.6 | 12.2 | 50.9 |
| 50-59 | 14.5 | 50.1 | 12.7 | 49.4 | 15.9 | 51.8 |
| 60-69 | 11.2 | 52.5 | 12.1 | 52.4 | 12.6 | 53.6 |
| 70-79 | 8.3 | 55.2 | 9.7 | 57.2 | 8.8 | 56.6 |
| 80-89 | 4.5 | 60.9 | 3.6 | 64.7 | 6.5 | 61.3 |
| 90+ | 1.2 | 71.5 | 0.6 | 73.5 | 1.2 | 73.3 |
| **Population covered** | **100.0** | 50.9 | **100.0** | 50.7 | **88.2** | 51.8 |

| Country | LITHUANIA | | ROMAGNA | | SCOTLAND | |
|---|---|---|---|---|---|---|
| Age (years) | % | % female | % | % female | % | % female |
| 0-9 | 10.4 | 48.7 | 8.1 | 48.2 | 10.3 | 48.6 |
| 10-19 | 9.4 | 48.8 | 9.2 | 48.3 | 10.6 | 49.0 |
| 20-29 | 12.2 | 47.8 | 9.2 | 48.1 | 13.2 | 49.6 |
| 30-39 | 12.9 | 47.4 | 10.8 | 50.5 | 13.4 | 50.7 |
| 40-49 | 13.2 | 50.3 | 15.6 | 50.4 | 12.3 | 51.2 |
| 50-59 | 15.0 | 53.1 | 16.0 | 50.6 | 14.5 | 51.7 |
| 60-69 | 12.6 | 57.9 | 12.3 | 52.5 | 11.9 | 51.7 |
| 70-79 | 8.5 | 65.5 | 10.3 | 53.9 | 8.9 | 53.5 |
| 80-89 | 5.9† | 73.1† | 6.8 | 58.9 | 4.2 | 59.4 |
| 90+ | | | 1.6 | 70.8 | 0.8 | 68.8 |
| **Population covered** | **100.0** | 53.3 | **100.0** | 51.4 | **100.0** | 51.2 |

| Country | SLOVENIA | | SWEDEN | |
|---|---|---|---|---|
| Age (years) | % | % female | % | % female |
| 0-9 | 9.8 | 48.4 | 11.7 | 48.5 |
| 10-19 | 9.7 | 48.5 | 11.6 | 48.4 |
| 20-29 | 10.2 | 45.9 | 12.5 | 47.8 |
| 30-39 | 13.4 | 46.5 | 13.5 | 48.7 |
| 40-49 | 14.9 | 47.1 | 12.5 | 49.1 |
| 50-59 | 14.3 | 49.2 | 12.6 | 49.3 |
| 60-69 | 13.4 | 50.7 | 10.7 | 50.2 |
| 70-79 | 8.8 | 55.0 | 9.7 | 51.6 |
| 80-89 | 4.7 | 64.0 | 4.3 | 57.1 |
| 90+ | 0.9 | 76.6 | 1.0 | 69.6 |
| **Population covered** | **99.0** | 49.7 | **100.0** | 49.7 |

Note: Age (years) – age distribution of covered population; † percentage for age group 80+

**Table S3**: Changes between the COVID period and the immediately preceding period in the ten therapeutic subgroups (ATC level 2) of prescription drugs with the highest dispensed volumes (measured by DDD per 1000 inhabitants per day (DDD/TID)) across eight European countries/regions

Therapeutic subgroups shown:

| | | | |
|---|---|---|---|
| A02 | Drugs for acid related disorders | C08 | Calcium channel blockers |
| A10 | Drugs used in diabetes | C09 | Agents acting on the renin-angiotensin system |
| B01 | Antithrombotic agents | C10 | Lipid modifying agents |
| B03 | Antianemic preparations | N06 | Psychoanaleptics |
| C07 | Beta blocking agents | R03 | Drugs for obstructive airway diseases |

| | | Dispensed volume (DDD/TID) | | | | |
|---|---|---|---|---|---|---|
| Country | ATC | Period 1 (Mar 2017–Feb 2018) | Period 2 (Mar 2018–Feb 2019) | Period 3 (pre-COVID period, Mar 2019–Feb 2020) | Period 4 (COVID period, Mar 2020–Feb 2021) | Change in period 4 relative to period 3 (%) |
| Catalonia | A02 | 102.3 | 100.2 | 99.6 | 96.3 | -3.3 |
| | A10 | 69.3 | 69.1 | 70.1 | 69.7 | -0.6 |
| | B01 | 64.3 | 63.1 | 68.3 | 67.7 | -0.8 |
| | B03 | 75.2 | 77.4 | 79.5 | 76.9 | -3.1 |
| | C07 | 23.9 | 23.2 | 23.1 | 22.6 | -1.8 |
| | C08 | 41.7 | 41.8 | 42.7 | 42.4 | -0.6 |
| | C09 | 204.4 | 203.4 | 204.5 | 201.1 | -1.7 |
| | C10 | 99.4 | 104.5 | 104.2 | 106.5 | 2.2 |
| | N06 | 88.4 | 89.8 | 92.7 | 93.3 | 0.7 |
| | R03 | 49.9 | 49.9 | 48.3 | 44.3 | -8.2 |
| Czechia | A02 | 72.4 | 74.2 | 76.9 | 76.3 | -0.7 |
| | A10 | 89.9 | 90.3 | 92.7 | 93.0 | 0.4 |
| | B01 | 94.2 | 94.4 | 95.7 | 96.2 | 0.5 |
| | B03 | 107.4 | 107.4 | 109.6 | 111.7 | 1.9 |
| | C07 | 66.6 | 64.1 | 62.9 | 61.0 | -3.2 |
| | C08 | 63.5 | 59.7 | 59.2 | 56.2 | -5.0 |
| | C09 | 253.9 | 250.9 | 253.5 | 250.1 | -1.3 |
| | C10 | 135.3 | 143.3 | 154.5 | 166.5 | 7.8 |
| | N06 | 65.1 | 66.8 | 70.2 | 70.4 | 0.3 |
| | R03 | 52.6 | 52.5 | 52.9 | 53.1 | 0.3 |
| Germany | A02 | 146.2 | 138.8 | 134.5 | 133.1 | -1.0 |
| | A10 | 87.2 | 85.3 | 86.1 | 87.8 | 2.0 |
| | B01 | 68.6 | 68.2 | 69.4 | 70.3 | 1.3 |
| | B03 | 12.8 | 12.7 | 12.5 | 12.1 | -3.1 |
| | C07 | 85.7 | 80.8 | 78.6 | 76.9 | -2.1 |
| | C08 | 87.2 | 85.7 | 89.2 | 91.6 | 2.8 |
| | C09 | 356.0 | 352.4 | 363.2 | 368.5 | 1.5 |
| | C10 | 91.6 | 94.1 | 100.8 | 109.0 | 8.2 |
| | N06 | 66.4 | 65.4 | 66.1 | 67.1 | 1.5 |
| | R03 | 52.9 | 50.8 | 50.4 | 49.9 | -1.0 |

(continued)

**Table S3**: Changes between the COVID period and the immediately preceding period in the ten therapeutic subgroups (ATC level 2) of prescription drugs with the highest dispensed volumes (measured by DDD per 1000 inhabitants per day (DDD/TID)) across eight European countries/regions (continued)

| | | Dispensed volume (DDD/TID) | | | | |
|---|---|---|---|---|---|---|
| Country | ATC | Period 1 (Mar 2017– Feb 2018) | Period 2 (Mar 2018– Feb 2019) | Period 3 (pre-COVID period, Mar 2019– Feb 2020) | Period 4 (COVID period, Mar 2020– Feb 2021) | Change in period 4 relative to period 3 (%) |
| Lithuania | A02 | 34.8 | 33.9 | 34.9 | 38.2 | 9.3 |
| | A10 | 51.8 | 54.7 | 58.0 | 59.8 | 3.1 |
| | B01 | 22.8 | 26.3 | 29.5 | 30.7 | 3.9 |
| | B03 | 3.3 | 3.2 | 3.7 | 3.3 | -9.2 |
| | C07 | 79.0 | 80.9 | 83.1 | 84.7 | 1.9 |
| | C08 | 28.5 | 28.3 | 28.6 | 26.7 | -6.7 |
| | C09 | 217.8 | 222.3 | 229.2 | 227.4 | -0.8 |
| | C10 | 39.9 | 47.8 | 64.0 | 75.9 | 18.7 |
| | N06 | 52.8 | 54.1 | 58.1 | 59.9 | 3.2 |
| | R03 | 33.6 | 33.2 | 34.7 | 34.2 | -1.6 |
| Romagna | A02 | 58.9 | 59.3 | 57.5 | 55.7 | -3.2 |
| | A10 | 62.5 | 63.1 | 64.1 | 61.5 | -4.1 |
| | B01 | 108.2 | 110.2 | 112.1 | 105.6 | -5.7 |
| | B03 | 12.7 | 11.9 | 17.8 | 26.4 | 48.5 |
| | C07 | 57.4 | 57.6 | 57.9 | 57.3 | -1.0 |
| | C08 | 56.6 | 56.5 | 57.2 | 57.2 | -0.1 |
| | C09 | 237.0 | 236.4 | 235.6 | 231.6 | -1.7 |
| | C10 | 98.8 | 101.4 | 104.8 | 106.0 | 1.1 |
| | N06 | 49.7 | 51.0 | 51.3 | 50.8 | -0.9 |
| | R03 | 35.3 | 35.1 | 34.8 | 29.9 | -14.1 |
| Scotland | A02 | 144.3 | 145.8 | 149.1 | 148.5 | -0.4 |
| | A10 | 63.7 | 65.2 | 66.6 | 67.6 | 1.5 |
| | B01 | 81.5 | 81.1 | 80.8 | 81.2 | 0.6 |
| | B03 | 207.6 | 215.2 | 228.0 | 221.7 | -2.8 |
| | C07 | 38.2 | 37.8 | 37.4 | 36.9 | -1.3 |
| | C08 | 83.2 | 84.7 | 86.8 | 87.6 | 0.9 |
| | C09 | 208.1 | 208.3 | 209.1 | 207.2 | -0.9 |
| | C10 | 156.1 | 160.6 | 166.1 | 170.6 | 2.7 |
| | N06 | 145.3 | 153.8 | 163.2 | 170.4 | 4.4 |
| | R03 | 81.2 | 79.7 | 77.3 | 79.2 | 2.5 |

(continued)

**Table S3**: Changes between the COVID period and the immediately preceding period in the ten therapeutic subgroups (ATC level 2) of prescription drugs with the highest dispensed volumes (measured by DDD per 1000 inhabitants per day (DDD/TID)) across eight European countries/regions (continued)

| | | Dispensed volume (DDD/TID) | | | | |
|---|---|---|---|---|---|---|
| Country | ATC | Period 1 (Mar 2017–Feb 2018) | Period 2 (Mar 2018–Feb 2019) | Period 3 (pre-COVID period, Mar 2019–Feb 2020) | Period 4 (COVID period, Mar 2020–Feb 2021) | Change in period 4 relative to period 3 (%) |
| Slovenia | A02 | 68.8 | 70.9 | 73.5 | 73.9 | 0.5 |
| | A10 | 81.2 | 82.7 | 83.7 | 84.4 | 0.9 |
| | B01 | 97.1 | 98.3 | 98.9 | 98.9 | 0.0 |
| | B03 | 6.7 | 6.3 | 6.0 | 5.0 | -16.6 |
| | C07 | 44.6 | 44.9 | 44.8 | 44.2 | -1.3 |
| | C08 | 57.2 | 55.8 | 54.7 | 53.2 | -2.8 |
| | C09 | 250.7 | 247.3 | 243.4 | 236.1 | -3.0 |
| | C10 | 133.9 | 138.6 | 148.6 | 155.7 | 4.8 |
| | N06 | 67.8 | 70.5 | 72.6 | 71.7 | -1.2 |
| | R03 | 42.0 | 43.1 | 43.9 | 42.2 | -3.9 |
| Sweden | A02 | 65.2 | 64.3 | 65.5 | 64.9 | -0.8 |
| | A10 | 62.5 | 64.9 | 67.8 | 69.3 | 2.2 |
| | B01 | 85.2 | 85.2 | 85.7 | 85.0 | -0.8 |
| | B03 | 148.7 | 133.0 | 127.8 | 122.5 | -4.1 |
| | C07 | 48.1 | 47.1 | 46.6 | 45.5 | -2.3 |
| | C08 | 85.3 | 87.2 | 91.3 | 94.5 | 3.5 |
| | C09 | 180.1 | 183.3 | 189.6 | 193.0 | 1.8 |
| | C10 | 116.3 | 125.3 | 135.4 | 144.1 | 6.4 |
| | N06 | 115.3 | 118.7 | 123.8 | 126.8 | 2.5 |
| | R03 | 54.8 | 55.4 | 57.3 | 60.2 | 5.0 |

Tables S4 – S11 show for each of eight European countries/regions the ten therapeutic subgroups of prescription drugs with the greatest relative change in DDD per 1000 inhabitants per day (DDD/TID) in the COVID period (March 2020 – February 2021) compared to the same months one year before (period 3). The tables also show the main contributing chemical subgroups (ATC level 4) which together cover at least 2/3 of their respective therapeutic subgroup (ATC level 2) DDD volume.

**Table S4: Catalonia**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| G01 | G01AF | -15.7 | Imidazole derivatives |
| H02 | H02AB | -23.4 | Glucocorticoids |
| J01 | J01CA | -53.4 | Penicillins with extended spectrum |
| J01 | J01CR | -28.8 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01MA | -29.1 | Fluoroquinolones |
| J02 | J02AC | -28.4 | Triazole derivatives |
| J04 | J04AC | -29.3 | Hydrazides |
| J04 | J04AM | -10.8 | Combinations of drugs for treatment of tuberculosis |
| J06 | J06BA | 95.0 | Immunoglobulins, normal human |
| M01 | M01AE | -26.9 | Propionic acid derivatives |
| M03 | M03BX | -21.2 | Other centrally acting agents |
| P03 | P03AC | 31.2 | Pyrethrines, incl. synthetic compounds |
| R01 | R01AD | -18.6 | Corticosteroids |

**Table S5: Czechia**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A11 | A11CC | 18.6 | Vitamin D and analogues |
| B02 | B02AA | -61.0 | Amino acids |
| B02 | B02BA | -1.0 | Vitamin K |
| C04 | C04AD | -17.8 | Purine derivatives |
| C04 | C04AX | -5.5 | Other peripheral vasodilators |
| D01 | D01BA | -24.4 | Antifungals for systemic use |
| J01 | J01AA | -21.0 | Tetracyclines |
| J01 | J01CE | -57.9 | Beta-lactamase sensitive penicillins |
| J01 | J01CR | -33.2 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01DC | -46.8 | Second-generation cephalosporins |
| J01 | J01FA | -42.3 | Macrolides |
| J04 | J04AB | -18.2 | Antibiotics |
| J04 | J04AC | -26.1 | Hydrazides |
| J05 | J05AB | -0.1 | Nucleosides and nucleotides excl. reverse transcriptase inhibitors |
| J05 | J05AF | 2.0 | Nucleoside and nucleotide reverse transcriptase inhibitors |
| J05 | J05AR | -0.3 | Antivirals for treatment of HIV infections, combinations |
| P01 | P01BA | -9.9 | Aminoquinolines |
| R01 | R01AD | -17.7 | Corticosteroids |
| R05 | R05CB | -24.9 | Mucolytics |

**Table S6: Germany**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| C04 | C04AD | 6.9 | Purine derivatives |
| C04 | C04AX | -78.5 | Other peripheral vasodilators |
| D04 | D04AB | -40.3 | Anesthetics for topical use |
| D04 | D04AX | -30.1 | Other antipruritics |
| D08 | D08AE | 32.1 | Phenol and derivatives |
| J01 | J01AA | -12.8 | Tetracyclines |
| J01 | J01CA | -36.4 | Penicillins with extended spectrum |
| J01 | J01CR | -15.9 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01DC | -42.1 | Second-generation cephalosporins |
| J01 | J01FA | -52.5 | Macrolides |
| M02 | M02AA | -17.7 | Antiinflammatory preparations, non-steroids for topical use |
| M02 | M02AX | -22.6 | Other topical products for joint and muscular pain |
| P03 | P03AC | -20.7 | Pyrethrines, incl. synthetic compounds |
| P03 | P03AX | -49.6 | Other ectoparasiticides, incl. scabicides |
| R01 | R01AA | -50.4 | Sympathomimetics, plain |
| R01 | R01AD | -6.0 | Corticosteroids |
| R02* | R02AB | -46.9 | Antibiotics |
| R05 | R05CA | -50.8 | Expectorants |
| R05 | R05CB | -29.0 | Mucolytics |
| S02 | S02AA | -25.4 | Antiinfectives |
| S02 | S02CA | -11.1 | Corticosteroids and antiinfectives in combination |

* R02AB covers only 29% of R02 DDD volume, other ATC level 4 subgroups are Germany-specific groups not listed in the WHO ATC classification.

**Table S7: Lithuania**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A02 | A02BC | 17.6 | Proton pump inhibitors |
| D01 | D01BA | -19.5 | Antifungals for systemic use |
| G02 | G02BB | -9.8 | Intravaginal contraceptives |
| J01 | J01AA | 0.9 | Tetracyclines |
| J01 | J01CA | -40.6 | Penicillins with extended spectrum |
| J01 | J01CE | -77.0 | Beta-lactamase sensitive penicillins |
| J01 | J01CR | -33.3 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01EE | -52.3 | Combinations of sulfonamides and trimethoprim, incl. derivatives |
| J01 | J01FA | -41.2 | Macrolides |
| J02 | J02AC | -13.6 | Triazole derivatives |
| N02 | N02AB | 2.7 | Phenylpiperidine derivatives |
| N02 | N02CC | 20.6 | Selective serotonin (5HT1) agonists |
| P01 | P01BA | 20.5 | Aminoquinolines |
| P02 | P02CA | -22.6 | Benzimidazole derivatives |
| R01 | R01AD | -34.4 | Corticosteroids |
| R06 | R06AX | -9.9 | Other antihistamines for systemic use |

**Table S8: Romagna**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A12 | A12AA | -49.9 | Calcium |
| A12 | A12AX | -26.1 | Calcium, combinations with vitamin D and/or other drugs |
| D01 | D01BA | -21.8 | Antifungals for systemic use |
| D07 | D07AC | 6.7 | Corticosteroids, potent (group III) |
| D07 | D07AD | 44.3 | Corticosteroids, very potent (group IV) |
| D10 | D10BA | 16.0 | Retinoids for treatment of acne |
| J01 | J01CA | -50.5 | Penicillins with extended spectrum |
| J01 | J01CR | -41.4 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01FA | -47.0 | Macrolides |
| J02 | J02AC | -16.4 | Triazole derivatives |
| J04 | J04AB | -21.8 | Antibiotics |
| J04 | J04AC | -24.1 | Hydrazides |
| L02 | L02AE | -10.2 | Gonadotropin releasing hormone analogues |
| L02 | L02BG | -14.5 | Aromatase inhibitors |
| P02 | P02CA | -26.8 | Benzimidazole derivatives |
| R03 | R03AK | -0.1 | Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics |
| R03 | R03BA | -51.8 | Glucocorticoids |
| R03 | R03BB | -10.5 | Anticholinergics |

**Table S9: Scotland**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A01 | A01AB | -16.0 | Antiinfectives and antiseptics for local oral treatment |
| A08 | A08AB | -26.9 | Peripherally acting antiobesity products |
| A12 | A12AA | 8.4 | Calcium |
| D01 | D01BA | -38.9 | Antifungals for systemic use |
| G03 | G03AC | -44.3 | Progestogens |
| G03 | G03CA | 1.9 | Natural and semisynthetic estrogens, plain |
| H01 | H01BA | -11.3 | Vasopressin and analogues |
| H02 | H02AB | -14.5 | Glucocorticoids |
| J01 | J01AA | -12.0 | Tetracyclines |
| J01 | J01CA | -29.1 | Penicillins with extended spectrum |
| J01 | J01FA | -20.2 | Macrolides |
| J02 | J02AC | -12.9 | Triazole derivatives |
| R01 | R01AD | -8.0 | Corticosteroids |

**Table S10: Slovenia**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A11 | A11CC | 45.7 | Vitamin D and analogues |
| B02 | B02AA | 9.9 | Amino acids |
| B02 | B02BX | 11.8 | Other systemic hemostatics |
| B03 | B03AA | -15.0 | Iron bivalent, oral preparations |
| B03 | B03AB | -25.3 | Iron trivalent, oral preparations |
| D01 | D01BA | -33.8 | Antifungals for systemic use |
| D10 | D10BA | -12.2 | Retinoids for treatment of acne |
| G01 | G01AF | -10.3 | Imidazole derivatives |
| J01 | J01CA | -51.9 | Penicillins with extended spectrum |
| J01 | J01CE | -59.8 | Beta-lactamase sensitive penicillins |
| J01 | J01CR | -21.1 | Combinations of penicillins, incl. beta-lactamase inhibitors |
| J01 | J01FA | -36.5 | Macrolides |
| J02 | J02AC | -15.5 | Triazole derivatives |
| P02 | P02CA | -18.6 | Benzimidazole derivatives |
| R01 | R01AD | -16.9 | Corticosteroids |

**Table S11: Sweden**

| ATC level 2 | ATC level 4 | Change between COVID period and pre-COVID period (%) | Chemical subgroup |
|---|---|---|---|
| A01 | A01AA | -25.3 | Caries prophylactic agents |
| A03 | A03AX | -3.5 | Other drugs for functional gastrointestinal disorders |
| A03 | A03FA | -1.7 | Propulsives |
| A11 | A11CC | 14.3 | Vitamin D and analogues |
| C02 | C02CA | 13.1 | Alpha-adrenoreceptor antagonists |
| D01 | D01BA | -15.1 | Antifungals for systemic use |
| D05 | D05BB | -6.6 | Retinoids for treatment of psoriasis |
| D11 | D11AX | 17.1 | Other dermatologicals |
| J01 | J01AA | -13.7 | Tetracyclines |
| J01 | J01CA | -17.2 | Penicillins with extended spectrum |
| J01 | J01CE | -34.8 | Beta-lactamase sensitive penicillins |
| J01 | J01CF | -9.6 | Beta-lactamase resistant penicillins |
| R01 | R01AD | -4.8 | Corticosteroids |
| R03 | R03AC | 1.7 | Selective beta-2-adrenoreceptor agonists |
| R03 | R03AK | 8.6 | Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics |
| R03 | R03BA | 5.5 | Glucocorticoids |

Figures S3 and S4 show relative changes in the top ten therapeutic subgroups with highest dispensed volume (in the pre-COVID period) across eight European countries/regions split in half-years.

Legend for Figures S3 and S4:

Country codes:

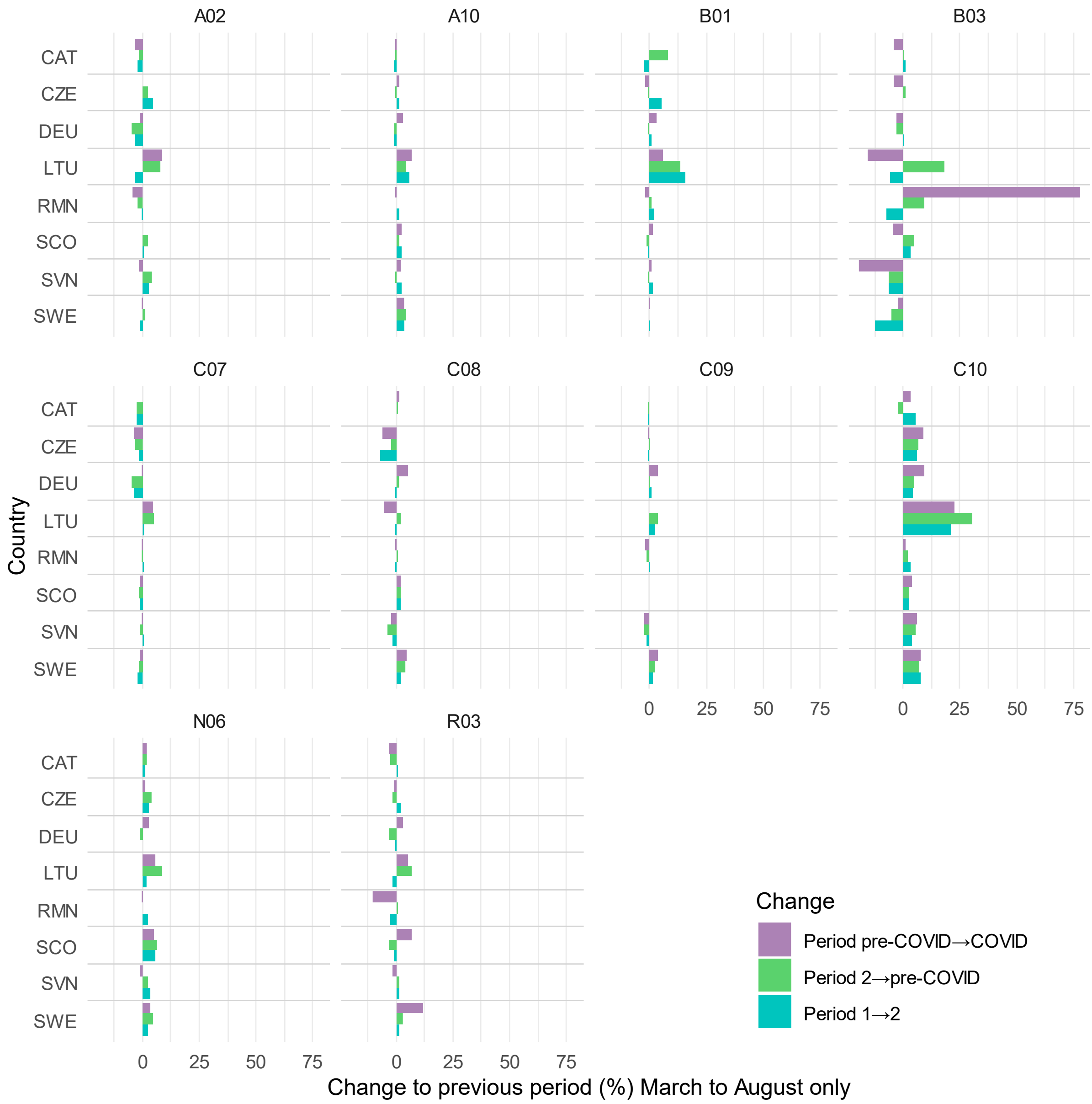
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAT | Catalonia | CZE | Czechia | DEU | Germany | LTU | Lithuania |
| RMN | Romagna | SCO | Scotland | SVN | Slovenia | SWE | Sweden |

Therapeutic subgroups:

| | | | |
|---|---|---|---|
| A02 | Drugs for acid related disorders | C08 | Calcium channel blockers |
| A10 | Drugs used in diabetes | C09 | Agents acting on the renin-angiotensin system |
| B01 | Antithrombotic agents | C10 | Lipid modifying agents |
| B03 | Antianemic preparations | N06 | Psychoanaleptics |
| C07 | Beta blocking agents | R03 | Drugs for obstructive airway diseases |

Note: B03 - change of reimbursement rules in Romagna: since September 2019 the package of folic acid (B03BB01) 5mg with 120 tablets has been included in the list of reimbursed medicines whereas before only smaller packages were reimbursed.

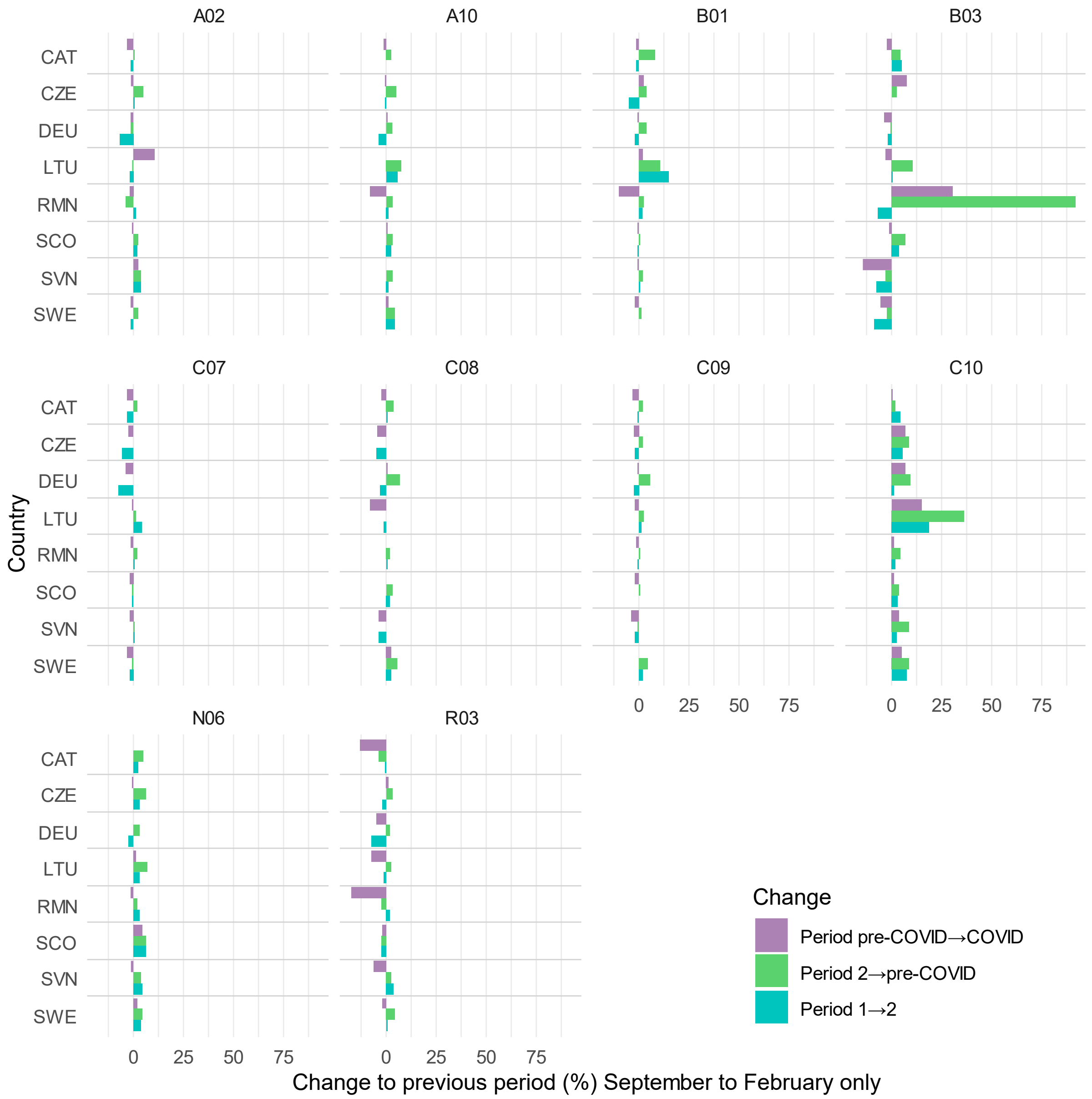
Figure S3: Top ten therapeutic subgroups with highest dispensed volume (in the pre-COVID period) across eight European countries/regions: relative change of DDD/TID between four 6-month periods March to August in 2017 to 2020




Legend for Figure S3:

Periods:
Period 1: March 2017 – August 2017
Period 2: March 2018 – August 2018
Pre-COVID period: March 2019 – August 2019
COVID period: March 2020 – August 2020

Figure S4: Top ten therapeutic subgroups with highest dispensed volume (in the pre-COVID period) across eight European countries/regions: relative change of DDD/TID between four 6-month periods September to February in 2017 to 2021




Legend for Figure S4:

Periods:
Period 1: September 2017 – February 2018
Period 2: September 2018 – February 2019
Pre-COVID period: September 2019 – February 2020
COVID period: September 2020 – February 2021

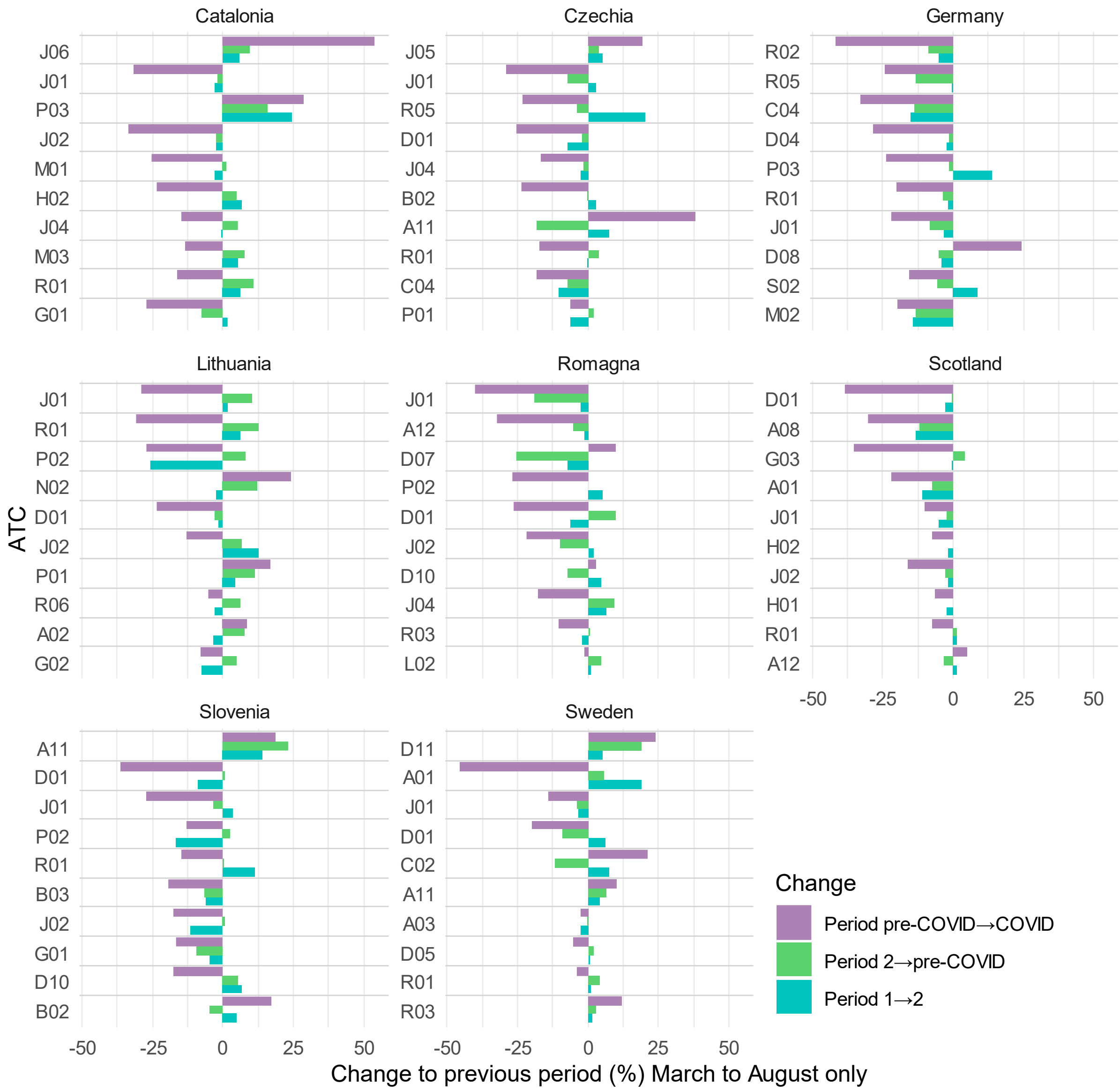
Figures S5 and S6 show relative changes in the top ten therapeutic subgroups with most marked relative change in DDD/TID volume (in the COVID period relative to the pre-COVID period) across eight European countries/regions split in half-years.

Legend for Figures S5 and S6:

Therapeutic subgroups

| | | | |
|---|---|---|---|
| A01 | Stomatological preparations | H02 | Corticosteroids for systemic use |
| A02 | Drugs for acid related disorders | J01 | Antibacterials for systemic use |
| A03 | Drugs for functional gastrointestinal disorders | J02 | Antimycotics for systemic use |
| A08 | Antiobesity preparations, excl. diet products | J04 | Antimycobacterials |
| A11 | Vitamins | J05 | Antivirals for systemic use |
| A12 | Mineral supplements | J06 | Immune sera and immunoglobulins |
| B02 | Antihemorrhagics | L02 | Endocrine therapy |
| B03 | Antianemic preparations | M01 | Antiinflammatory and antirheumatic products |
| C02 | Antihypertensives | M02 | Topical products for joint and muscular pain |
| C04 | Peripheral vasodilators | M03 | Muscle relaxants |
| D01 | Antifungals for dermatological use | N02 | Analgesics |
| D04 | Antipruritics, incl. antihistamines, anesthetics, etc. | P01 | Antiprotozoals |
| D05 | Antipsoriatics | P02 | Anthelmintics |
| D07 | Corticosteroids, dermatological preparations | P03 | Ectoparasiticides, incl. scabicides, insecticides and repellents |
| D08 | Antiseptics and disinfectants | R01 | Nasal preparations |
| D10 | Anti-acne preparations | R02 | Throat preparations |
| D11 | Other dermatological preparations | R03 | Drugs for obstructive airway diseases |
| G01 | Gynecological antiinfectives and antiseptics | R05 | Cough and cold preparations |
| G02 | Other gynecologicals | R06 | Antihistamines for systemic use |
| G03 | Sex hormones and modulators of the genital system | S02 | Otologicals |
| H01 | Pituitary and hypothalamic hormones and analogues | | |

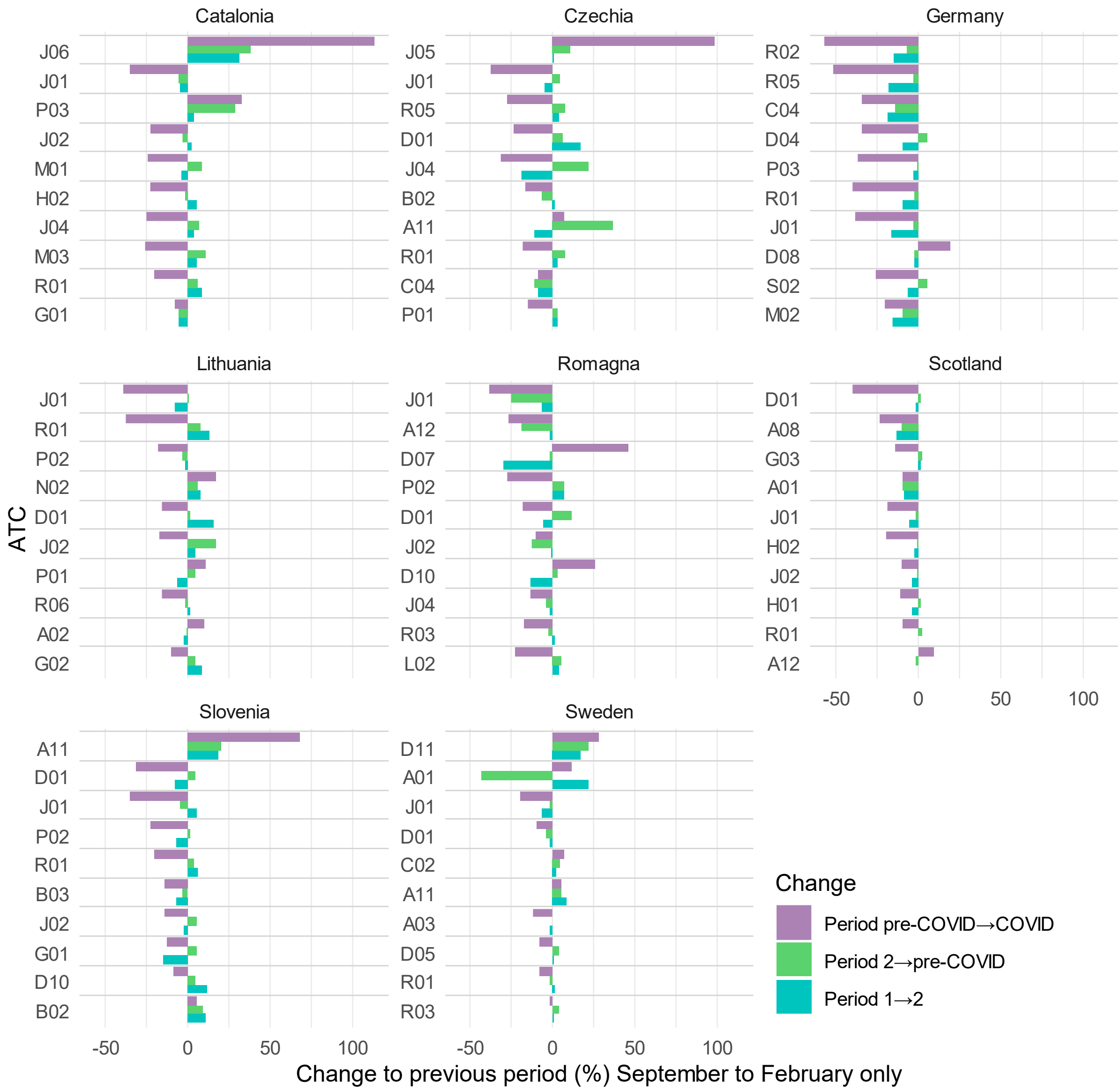
Figure S5: Top ten therapeutic subgroups with most marked relative change in DDD/TID volume (in the COVID period relative to pre-COVID period) across eight European countries/regions: relative change of DDD/TID between four 6-month periods March to August in 2017 to 2020




Legend for Figure S5:

Periods:
Period 1: March 2017 – August 2017
Period 2: March 2018 – August 2018
Pre-COVID period: March 2019 – August 2019
COVID period: March 2020 – August 2020

Figure S6: Top ten therapeutic subgroups with most marked relative change in DDD/TID volume (in the COVID period relative to pre-COVID period) across eight European countries/regions: relative change of DDD/TID between four 6-month periods September to February in 2017 to 2021




Legend for Figure S6:

Periods:
Period 1: September 2017 – February 2018
Period 2: September 2018 – February 2019
Pre-COVID period: September 2019 – February 2020
COVID period: September 2020 – February 2021

## Time series analysis

Figures S7 and S8 show ARIMA models of total market development (in DDD/TID) in eight European countries/regions. Details of the models with the pandemic impact assessment are in Table S12.

Legend for Figures S7 and S8:

Black line – time series (actual values)

Red vertical line – onset of the pandemic

Grey line – ARIMA model (accounting for long-term effect of the COVID-19 pandemic and its short-term stockpiling effect in the first three months of pandemic)

Blue line – prediction on the base of the ARIMA model for data before the onset of the pandemic

Violet strips – confidence intervals (CI) of predictions (on the base of the ARIMA model for data before the onset of the pandemic). Darker violet: 80% CI, lighter violet: 95% CI.

Figure S7:

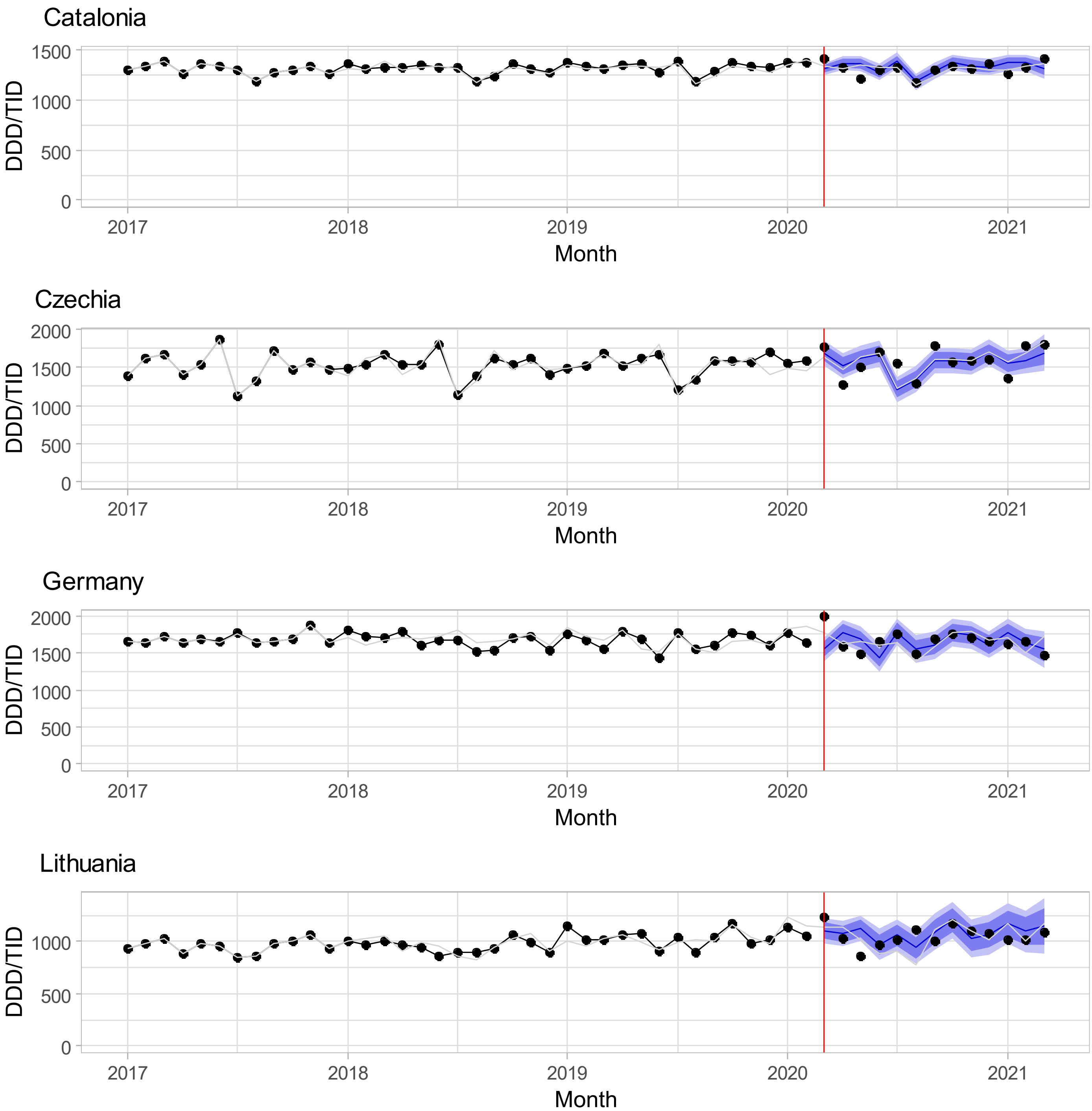
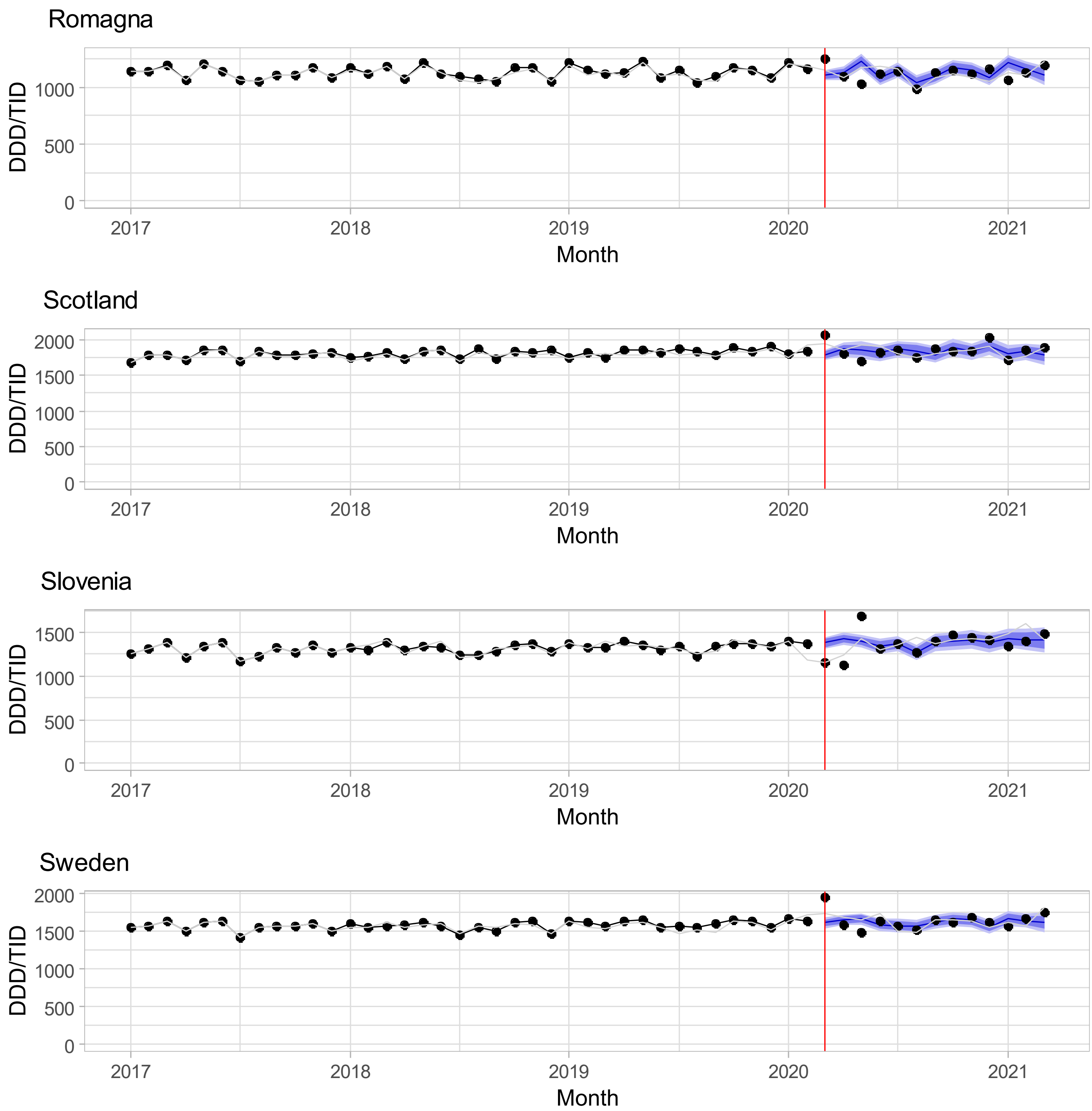

Catalonia
DDD/TID
1500
1000
500
0
2017
2018
2019
2020
2021
Month
Czechia
DDD/TID
2000
1500
1000
500
0
2017
2018
2019
2020
2021
Month
Germany
DDD/TID
2000
1500
1000
500
0
2017
2018
2019
2020
2021
Month
Lithuania
DDD/TID
1000
500
0
2017
2018
2019
2020
2021
Month

Figure S8:


Romagna
DDD/TID
0
500
1000
2017
2018
2019
2020
2021
Month
Scotland
DDD/TID
0
500
1000
1500
2000
2017
2018
2019
2020
2021
Month
Slovenia
DDD/TID
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2017
2018
2019
2020
2021
Month
Sweden
DDD/TID
0
500
1000
1500
2000
2017
2018
2019
2020
2021
Month

**Table S12**: Details on the ARIMA models used for impact assessment of the pandemic on global dispensed volume of prescription drugs

| Country/region | Model | Parameter | Estimated value | Standard error | P-value† |
|---|---|---|---|---|---|
| Catalonia | $ARIMA(0,0,2)(0,1,0)_{12}$ | ma1 | –0.538 | 0.159 | <0.001 |
| | | ma2 | 0.333 | 0.212 | 0.118 |
| | | long-term | –31.811 | 9.449 | <0.001 |
| | | short-term | 43.383 | 14.874 | <0.001 |
| Czechia | $ARIMA(0,0,0)(0,1,0)_{12}$ | long-term | 16.109 | 32.430 | 0.619 |
| | | short-term | –70.985 | 50.240 | 0.158 |
| Germany | $ARIMA(0,0,3)(0,1,0)_{12}$ | ma1 | –0.645 | 0.172 | <0.001 |
| | | ma2 | 0.384 | 0.215 | 0.074 |
| | | ma3 | 0.526 | 0.170 | 0.002 |
| | | long-term | –33.974 | 31.589 | 0.282 |
| | | short-term | 117.292 | 24.906 | <0.001 |
| Lithuania | $ARIMA(2,1,0)(0,1,0)_{12}$ | ar1 | –0.803 | 0.144 | <0.001 |
| | | ar2 | –0.560 | 0.136 | <0.001 |
| | | long-term | –38.237 | 62.662 | 0.542 |
| | | short-term | 109.461 | 44.051 | <0.001 |
| Romagna | $ARIMA(2,0,0)(0,1,0)_{12}$ | ar1 | –0.620 | 0.140 | <0.001 |
| | | ar2 | –0.466 | 0.137 | <0.001 |
| | | long-term | –29.078 | 6.190 | <0.001 |
| | | short-term | 47.029 | 11.958 | <0.001 |
| Scotland | $ARIMA(0,0,2)(0,1,0)_{12}$ | ma1 | –0.547 | 0.160 | <0.001 |
| | | ma2 | 0.471 | 0.148 | 0.001 |
| | | long-term | –13.899 | 16.794 | 0.408 |
| | | short-term | 116.710 | 25.047 | <0.001 |
| Slovenia | $ARIMA(2,1,0)(0,1,0)_{12}$ | ar1 | –0.893 | 0.131 | <0.001 |
| | | ar2 | –0.637 | 0.133 | <0.001 |
| | | long-term | –74.580 | 52.878 | 0.158 |
| | | short-term | –168.937 | 35.744 | <0.001 |
| Sweden | $ARIMA(3,0,0)(0,1,0)_{12}$ | ar1 | –0.359 | 0.147 | 0.014 |
| | | ar2 | –0.105 | 0.161 | 0.514 |
| | | ar3 | 0.383 | 0.153 | 0.012 |
| | | long-term | 2.222 | 17.613 | 0.900 |
| | | short-term | 113.902 | 25.272 | <0.001 |

Note: †z-test

Parameters: ma1 – first order moving average, ma2 – second order moving average, ma3 – third order moving average, ar1 – first order autoregression, ar2 – second order autoregression, long-term – lasting effect of the pandemic, short-term – short duration effect of the onset of the pandemic.

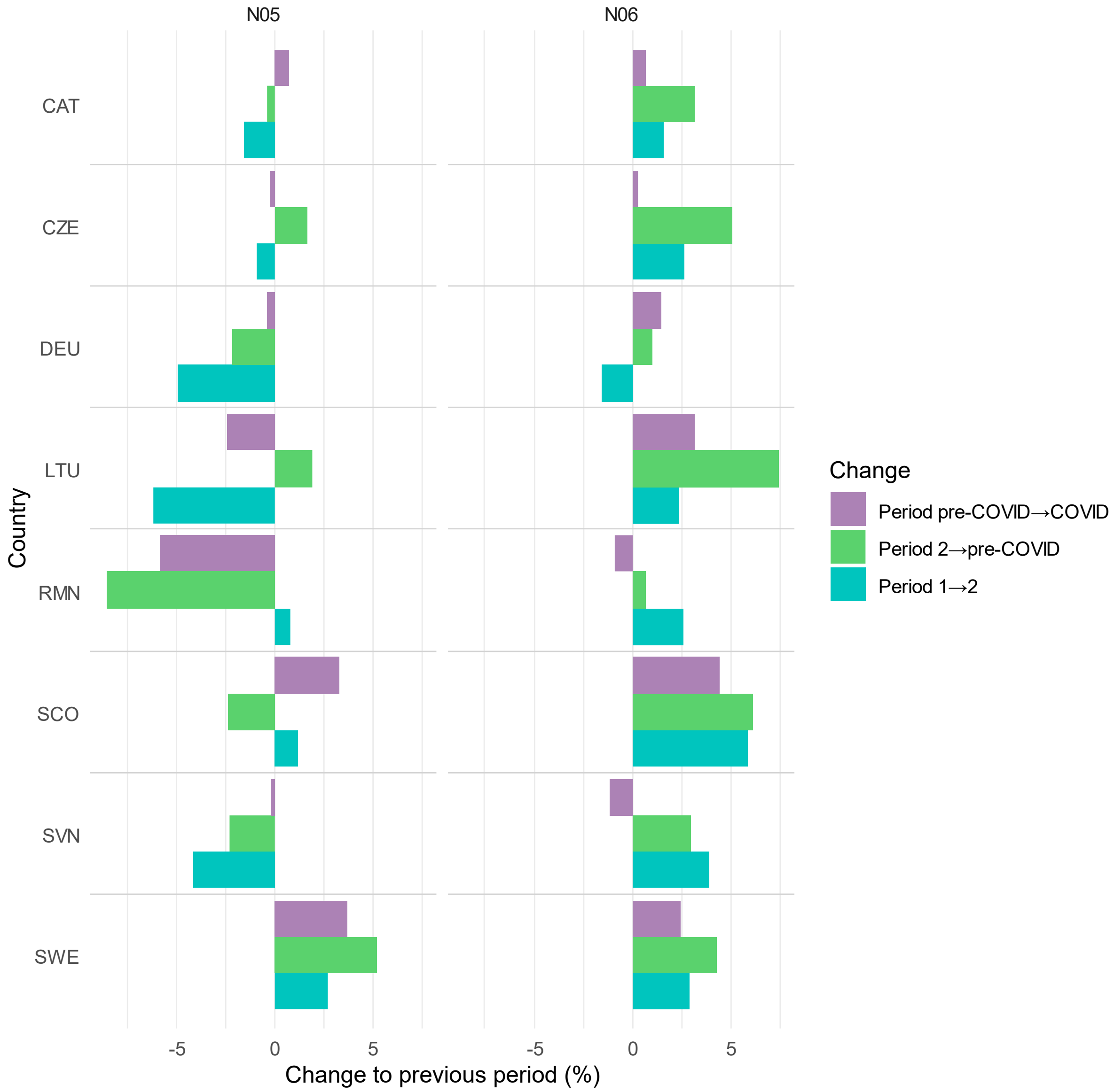
For Czechia, the used final model had a significant Ljung-Box test, which means that residuals were not completely free of autocorrelation, however, we did not manage to find a better parsimonious model.

**Table S13**: Change (%) in average therapeutic quantity per pack ($\Delta u$) broken down to changes of average therapeutic quantity per pack within chemical subgroups ($\Delta v$) and change of market shares of the chemical subgroups ($\Delta s$) for eight European countries/regions, September to February in the years 2017 to 2021; chemical subgroups at ATC level 4

| Baseline: | 9/2017 to 2/2018 | | | 9/2018 to 2/2019 | | | 9/2019 to 2/2020 | | |
|---|---|---|---|---|---|---|---|---|---|
| Outcome period: | 9/2018 to 2/2019 | | | 9/2019 to 2/2020 | | | 9/2020 to 2/2021 | | |
| Country | $\Delta v$ | $\Delta s$ | $\Delta u$ | $\Delta v$ | $\Delta s$ | $\Delta u$ | $\Delta v$ | $\Delta s$ | $\Delta u$ |
| Catalonia | 1.013 | 1.001 | 1.014 | 1.004 | 1.000 | 1.004 | 1.011 | 1.013 | 1.024 |
| Czechia | 1.018 | 0.994 | 1.011 | 1.024 | 1.003 | 1.027 | 1.038 | 1.019 | 1.058 |
| Germany | 1.002 | 1.014 | 1.016 | 1.001 | 1.012 | 1.014 | 1.011 | 1.048 | 1.059 |
| Lithuania | 1.006 | 1.004 | 1.010 | 1.014 | 0.997 | 1.011 | 0.986 | 1.014 | 1.000 |
| Romagna | 1.001 | 1.003 | 1.005 | 1.026 | 1.016 | 1.043 | 1.027 | 1.019 | 1.047 |
| Scotland | 1.003 | 1.010 | 1.013 | 0.997 | 1.007 | 1.004 | 1.009 | 1.013 | 1.022 |
| Slovenia | 1.025 | 0.993 | 1.018 | 1.029 | 1.002 | 1.031 | 1.068 | 1.009 | 1.077 |
| Sweden | 0.995 | 1.011 | 1.006 | 1.008 | 1.005 | 1.012 | 1.004 | 1.013 | 1.017 |

Note: For the sake of better legibility we show the values $\delta v = \Delta v - 1$, $\delta s = \Delta s - 1$, and $\delta u = \Delta u - 1$.

Figure S9: Psycholeptics and psychoanaleptics: relative change of DDD/TID between four periods across eight European countries/regions




Legend for Figure S9:

Periods:
Period 1: March 2017 – February 2018
Period 2: March 2018 – February 2019
Pre-COVID period: March 2019 – February 2020
COVID period: March 2020 – February 2021

Country codes:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CAT | Catalonia | CZE | Czechia | DEU | Germany | LTU | Lithuania |
| RMN | Romagna | SCO | Scotland | SVN | Slovenia | SWE | Sweden |

Therapeutic subgroups:

| | | | |
|---|---|---|---|
| N05 | Psycholeptics | N06 | Psychoanaleptics |