Utrecht University

Pharmacoepidemiology and
Clinical Pharmacology

STUDY PROTOCOL

The Impact of COVID-19 Pandemic on Drug Use: Implications for Regulatory Intervention Impact Studies

Study information

Title	The Impact of COVID-19 Pandemic on Drug Use: Implications for Regulatory Intervention Impact Studies
Protocol version identifier	v1.0
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Medicinal product(s)	Multiple (see section 9.3.3)
Research question	To assess whether the short- and/or long-term drug utilisation patterns were impacted by the COVID-19 pandemic.
Research objectives	• To describe the trends of prescribing various medicinal products from January 1, 2017, to December 31, 2022. The trends will be analysed by stratifying cohorts by age group, sex, and incident/prevalent use. The medicines will be assessed grouped based on higher levels of their ATC codes and individually. • -To identify potential structural breaks in prescribing patterns of selected medicinal products over time, which may indicate changes in the long-term trends • -To assess if structural breaks in trends (if they are present) align with restrictions implemented due to the COVID-19 pandemic (see section 9.3.4). • -To conduct sensitivity analyses to determine what assumptions reduce the probability of detecting structural breaks due to the COVID-19 pandemic in the secular trends of drug use (if they are present).
Authors	Tomas Lasys, Yared Santa-Ana-Tellez, Satu J. Siiskonen, Rolf H.H. Groenwold, Helga Gardarsdottir

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Abbreviations

ACE	Angiotensin-converting enzyme
ADR	Adverse drug reactions
AE	Adverse events
ARIMA	Autoregressive integrated moving average
ATC	Anatomical Therapeutic Chemical (classification system)
CPRD	Clinical Practice Research Datalink
DDD	Defined daily dose
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good pharmacovigilance practices
HMG CoA	β-Hydroxy β-methylglutaryl- Coenzyme A
ISPE	International Society for Pharmacoepidemiology
LT	Lithuania
NL	Kingdom of the Netherlands
PECP	Division of Pharmacoepidemiology & Clinical Pharmacology (Utrecht University)
RMM(s)	Risk mimisation measure(s)
SSRI(s)	Selective serotonin reuptake inhibitor(s)
TTP	Trusted third party
UK	United Kingdom
VDI	Virtual Desktop Infrastructure

1. Title

The Impact of COVID-19 Pandemic on Drug Use: Implications for Regulatory Intervention Impact Studies

2. Marketing authorisation holder

Non-applicable

3. Responsible parties

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4. Abstract

The Impact of COVID-19 Pandemic on Drug Use: Implications for Regulatory Intervention Impact Studies

– Authors

Tomas Lasys, Yared Santa-Ana-Tellez, Satu J. Siiskonen, Rolf H.H. Groenwold, Helga Gardarsdottir

– Rationale and background

In the European Union (EU), regulatory interventions known as risk minimisation measures (RMMs) are governed by the guidelines called Good pharmacovigilance practices (GVP). The current GVP guidelines also highlight the necessity to assess the impact of these regulatory interventions. However, in practice, the implementation of regulatory interventions depends on national and international authorities and might be affected by overlapping events, such as introducing a new competitor medicine. Medicine shortages can also cause perceived changes in medicine use. Therefore, it is challenging to discern whether the observed outcomes are directly caused by the

intervention or are part of pre-existing secular trends. The COVID-19 pandemic introduced additional complexity to drug utilisation patterns disrupting the usual prescription and dispensation of medicines which caused changes in drug utilisation and health outcome patterns.
In this study, we aim to explore whether the periods of strict pandemic restrictions (e.g. curfews and school closings) impacted drug utilisation patterns. Furthermore, we examine the implications of any disruptions for impact studies using data that includes the COVID pandemic period in the selected countries.

− Research question and objectives

Research question

- To assess whether the short- and/or long-term drug utilisation patterns were impacted by the COVID-19 pandemic.

Objectives:

- To describe the trends of prescribing various medicinal products from January 1, 2017, to December 31, 2022. The trends will be analysed by stratifying cohorts by age group, sex, and incident/prevalent use. The medicines will be assessed grouped based on higher levels of their ATC codes and individually.
- To identify potential structural breaks in prescribing patterns of selected medicinal products over time, which may indicate changes in the long-term trends
- To assess if structural breaks in trends (if they are present) align with restrictions implemented due to the COVID-19 pandemic (see section 9.3.4).
- To conduct sensitivity analyses to determine what assumptions reduce the probability of detecting structural breaks due to the COVID-19 pandemic in the secular trends of drug use (if they are present).

− Study design

The study design will be a retrospective population-based dynamic cohort study using time series analysis.

− Population

NL-PHARMO: a total (cumulative) number of persons with actual data is 10.0 million.

UK-CPRD: a total (cumulative) number of persons with actual data is 35.0 million.

LT-EPDB: a total (cumulative) number of persons with actual data is 2.6 million.

− *Variable*

The exposure of interest is the prescription or dispensing of biguanides (A10BA), sulfonylureas (A10BB), HMG CoA reductase inhibitors (C10AA), agents acting on the renin-angiotensin system (C09), selective serotonin reuptake inhibitors (N06AB), benzodiazepine derivatives (N05BA, N05CD), thyroid hormones (H03AA), beta-lactam antibacterials, penicillins (J01C), other beta-lactam antibacterials (J01D), sulphonamides and trimethoprim (J01E), macrolides, lincosamides, and streptogramins (J01FA), ivermectin (P02CF01, D11AX22), chloroquine and hydroxychloroquine (aminoquinolines: P01BA),

Other variables assessed include age, sex, country, and data source.

− *Data sources*

The study will include data sources from three countries: Netherlands - PHARMO (sample, nationally representative), the UK - CPRD, and Lithuania – electronic prescription database.

− *Study size*

NL-PHARMO: a total (cumulative) number of persons with actual data is 10.0 million.

UK-CPRD: a total (cumulative) number of persons with actual data is 35.0 million.

LT-EPDB: a total (cumulative) number of persons with actual data is 2.6 million.

− *Data analysis*

If information about prescribed/dispensed medicine package size, the number of units, and the prescribed daily dose data is missing, we will impute a duration based on either the most common duration for prescribing the specific medicines in clinical practice in the country or the duration based on the assumption that one defined daily dose (DDD) will be used per day.

All analyses will be stratified by drug group (based on ATC classification), database, and age group. Patients' characteristics at cohort entry will be summarised. Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimal and maximal values. Categorical variables will be described by the number and percentage of patients in each category.

An exploratory descriptive analysis will be conducted for each database separately. Baseline characteristics observed on the treatment initiation date will be summarised for each database. The statistical analyses will be carried out using ARIMA models for interrupted time series analysis.

5. Amendments and updates

Amendments and updates of the study protocol after the start of data collection:

Date	Amendment	Justification	Protocol Section

6. Milestones

Milestone	Planned date
Start of data extraction	July 15, 2023
End of data extraction	December 1, 2023
Final report of study results	December 1, 2024

7. Rationale and background

In the European Union (EU), regulatory interventions known as risk minimisation measures are implemented to ensure the protection of patients and public health [1]. The implementation of these regulatory interventions is described in a set of guidelines called Good pharmacovigilance practices (GVP). The current GVP guidelines also highlight the necessity to assess whether these regulatory interventions are effective in reaching the desired outcomes and offer considerations on conducting impact assessments of these regulatory interventions[2,3]. In practice, these impact assessments are most frequently performed using interrupted time series (ITS) design [4–6]. ITS study's primary measure usually is the step change in drug utilisation trends and/or change in a trend. However, how regulatory interventions are implemented depends on national and international authorities and might be affected by overlapping events such as the introduction of a new competitor or medicine shortages can also cause perceived changes in medicine use. Therefore, it is challenging to discern whether the observed outcomes are directly caused by the intervention or are part of pre-existing secular trends. This challenge is further deepened by the fact that many of the impact studies focus on all medicine users instead of only those specifically targeted by the regulatory intervention.

The COVID-19 pandemic introduced additional complexity to drug utilisation patterns disrupting the usual prescription and dispensation of medicines and causing changes in drug utilisation and health outcome patterns [7–9]. While the COVID-19 pandemic had global consequences, the impact of it was different in different countries and regions. Consequently, there is a need to account for these disruptions when conducting regulatory intervention studies. That includes consideration of the differences in response to the COVID-19 pandemic in different countries, and while some studies

have already assessed aggregated medicine use with regard to the COVID-19 pandemic, we want to focus on drug use data using ITS methods [10].

In this study, we aim to explore whether the periods of strict pandemic restrictions (e.g. curfews, workplace and school closings) might have an impact on drug utilisation patterns and what are the implications for impact studies using data that includes the COVID pandemic period in the selected countries.

8. Research question and objectives

Research question

- To assess whether the short- and/or long-term patterns of drug utilisation were impacted by the COVID-19 pandemic.

Objectives:

- To describe the trends of prescribing the selected medicinal products from January 1, 2017, to December 31, 2022. Trends will be analysed by stratifying cohorts by age group, sex, and incident/prevalent use. The medicines will be assessed grouped based on higher levels of their ATC codes and individually.
- To identify potential structural breaks in prescribing patterns of selected medicinal products over time, which may indicate changes in the long-term trends
- To assess if structural breaks in trends (if they are present) align with restrictions implemented due to the COVID-19 pandemic (see section 9.3.4).
- To conduct sensitivity analyses to determine what assumptions reduce the probability of detecting structural breaks due to the COVID-19 pandemic in the secular trends of drug use (if they are present).

9. Research methods

9.1. Study design

The study design will be a retrospective population-based dynamic cohort study. We will use interrupted time series analysis to identify the potential breaks in drug utilisation patterns before and during the COVID pandemic.

9.2. Setting

Data from three sources representing three countries will be used: PHARMO (the Netherlands), CPRD (the UK), and Lithuanian electronic prescription data (Lithuania) (see section 9.4. for details).

9.2.1. Study Period

The study period will be from January 1, 2017, until the latest available data cut-off (December 31, 2022, at the earliest).

9.2.2. Study population

The source population will include all persons of all ages registered in the selected data sources during the study period. The study's primary goal will be reached by creating cohorts of patients that receive the prescriptions of the selected medicines (see 9.3.3.) during any time of the study period (see section 9.2.1. for details)

Additional inclusion criteria:

- Continuous enrolment in the data source for more than 12 months before the first prescription of selected medicines.

9.2.3. Follow-up Period

The patient follow-up period begins at:

- Study start date (January 1, 2017) (if the patient was continuously enrolled in the database for 12 months at that time) or
- the date when a patient was continuously enrolled in the database for 12 months; whichever comes latest.

The patient follow-up period ends at:

- Date of patient death;
- Date of patient deregistration from a data provider (GP practice);
- Date of contributing data deregistration from available data sources;
- End of the study period (December 31 2022);
  Whichever comes first.

9.2.4. Subgroup analyses

Analyses will also be done in patient subgroups based on the following:

- Age:
  - <18 years of age

  - 18-64 years of age
  - ≥65 years of age
- Sex;
- Medicinal products for analyses will be grouped and analysed as therapeutic subgroups (3rd level in the ATC classification system), chemical subgroups (4th ATC level) and chemical substances (5th level).

9.3. Variables:

9.3.1. Demographics

- Sex
- Age (year of Rx − year of birth) will be assessed for each calendar year (population level) and each prescription.
- Data sources will be labelled as NL-PHARMO, UK-CPRD, LT-EPDB.

9.3.2. Selection choice for the study population

The goal of the selection of the medicines was to have a variety of medicines that have different indications and clinical treatment durations and that the medicine use would be well captured in prescription databases. We selected the medicines to be assessed based on their prevalent use in Europe and USA [11,12]. Finally, ACE inhibitors, ivermectin, chloroquine and hydroxychloroquine were included in our selection based on attention to these drugs during the COVID-19 pandemic [13–15].

Study cohorts obtained from different databases will be compared and described by reporting the relevant data and highlighting similarities and differences in the summarised results.

9.3.3. Exposure of interest

The study aims to assess drug utilisation trends of these selected medicines:

- Biguanides (A10BA),
- Sulfonylureas (A10BB),
- HMG CoA reductase inhibitors (C10AA),
- Agents acting on the renin-angiotensin system (C09) that include plain ACE inhibitors (C09AA), ACE inhibitors in combinations (C09BA, C09BB, C09BX), plain Angiotensin II receptor blockers (ARB) (C09CA), ACE inhibitors in combinations (C09DA, C09DB, C09DX), and renin inhibitors (C09XA),
- Selective serotonin reuptake inhibitors (N06AB),
- Benzodiazepine derivatives (N05BA, N05CD),

- Thyroid hormones (H03AA),
- Beta-lactam antibacterials, penicillins (J01C),
- Other beta-lactam antibacterials (J01D),
- Sulphonamides and trimethoprim (J01E),
- Macrolides, lincosamides, and streptogramins (J01FA),
- Ivermectin (P02CF01, D11AX22),
- Chloroquine and hydroxychloroquine (aminoquinolines: P01BA),

The code list of medicines is provided in Supplement 1. Drug exposure will be assessed using the prescription data and identifying medicines by ATC/BNF code and/or product/drug substance name.

9.3.3.1. Treatment initiation for all drug exposures

The treatment initiation date (index date) will be defined as the date of the prescription or dispensing of the study drugs during the follow-up period when a patient was not receiving that medication for at least 90 days (counting from the date of the calculated end of the last treatment episode). For antibiotics and ivermectin – when a patient was not receiving that medication for at least 30 days**.**

A shorter drug-free period is selected for antibiotics and ivermectin due to shorter treatment duration [16,17]. Longer periods will be assessed in the sensitivity analysis.

9.3.3.2. Duration of a treatment episode

The duration of the treatment episode will be estimated using the prescribed quantity based on package sizes, the number of units, and the prescribed daily dose. If these data are missing, we will impute a duration based on either the most common duration for prescribing the specific medicines in clinical practice in the country or the duration based on the assumption that one defined daily dose (DDD) will be used per day.

9.3.3.3. Treatment episodes with multiple prescriptions

The treatment episodes will be constructed in the case of multiple subsequent prescriptions[18]. If the start of the next prescription/dispensing of the same drug (the same ATC code) falls during the prior prescription/dispensing treatment or within 90 days after the end of the calculated treatment date (for antibiotics and ivermectin – 30 days), we will consider this as the start of that prescription. In case of overlap between prescription refills of the same medicine (i.e. a prescription refill with the same ATC/BNF code is given before the previous prescription runs out) will be accounted for by adding the overlapping days to the end of the treatment episode. In sensitivity analysis, we will explore treatment episodes if the subsequent prescription was for another drug of the same

therapeutic subgroup based on the ATC classification [19]. Variations of possible constructions of treatment episodes are depicted in **Figure 1.**

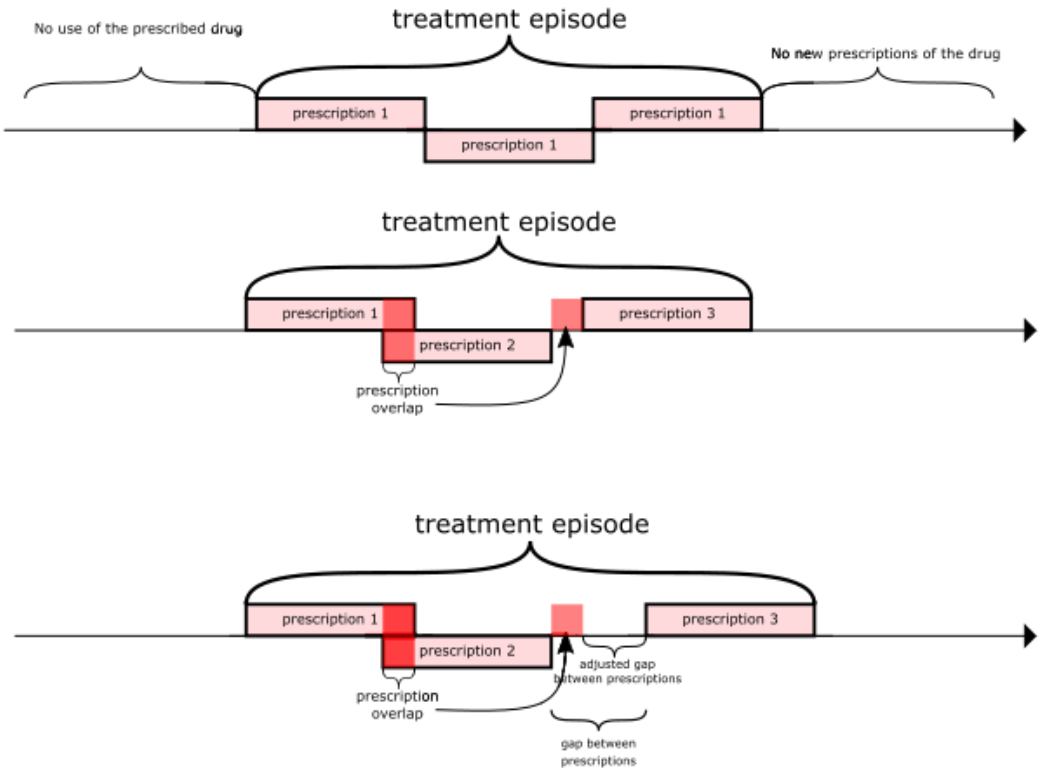

Figure 1 Possible variants of a single treatment episode with multiple prescriptions.

9.3.3.4. Incident and prevalent users

Initiators will be divided into the incident and prevalent users:

- Patients will be defined as incident users if no prescription or dispensing for the same drug is recorded for 90 days (for antibiotics and ivermectin – 30 days) prior to that prescription/dispensing or estimated treatment episode ended more than 90 days (for antibiotics and ivermectin – 30 days) prior to that prescription/dispensing, whichever comes latest.
- Patients prescribed drugs of interest but not classified as incident users will be considered prevalent users.

9.3.3.5. Prevalent patients with gaps between consecutive prescriptions

Patients receiving repeated prescriptions of the same less than 90 days from the end of the last treatment episode (for antibiotics and ivermectin –less than 30 days) will be counted as prevalent patients with gaps between prescriptions. In these cases, the period of up to 90 days (for antibiotics and ivermectin – 30 days) is considered a permissible gap. Based on the assumption that the

prescribed medicine has to be taken daily, we will estimate the patient's risk of having days without treatment before and during the periods of COVID-19 restrictions.

If prescriptions overlap (meaning a new prescription is dispensed before the expected end of the current one), the number of these overlapping days will be subtracted from the assumed gap between consecutive prescriptions. It will be regarded as the adjusted gap between consecutive prescriptions.

9.3.4. Response measures to the COVID-19 pandemic

The COVID-19 pandemic was met with a variety of different measures worldwide. For the purpose of this study, we focused on mandatory restrictions implemented on a national level. For these, we selected school, university and workplace closures mandated/implemented by the country governments. In the analysis, we will consider that the restrictions were implemented if at least one of the measures was implemented at that time. Information about the timing and type of COVID-19 restrictions for the Netherlands and Lithuania was taken from the Response Measures Database published by European Centre for Disease Prevention and Control (ECDC) [20]. The information about the restrictions in the UK was taken from Oxford COVID-19 Government Response Tracker [21].

The following COVID-19 pandemic restriction periods were defined:

- For the Netherlands:
    - From March 12, 2020, to June 16, 2020
    - From December 16, 2020, to April 24, 2021
    - From December 20, 2021, to January 14, 2022
- For Lithuania:
    - From March 16, 2020, to May 24, 2020
    - From November 7, 2020, to May 31, 2021
- For the UK:
    - From March 18, 2020, to August 12, 2020
    - From October 11, 2020, to November 08, 2020
    - From December 14, 2020, to April 11, 2021

Several of these mandatory national-level restrictions had transition periods where they were partially alleviated before they were lifted entirely. For sensitivity analysis, we will use extended COVID-19 restriction time windows by including these periods when at least one of the restrictions was partially upheld.
COVID-19 pandemic restriction periods will be:

- For the Netherlands:

  - From March 12, 2020, to September 1, 2020
  - From December 16, 2020, to August 8, 2021
  - From November 13, 2021, to February 24, 2022
- For Lithuania:
  - From March 16, 2020, to June 30, 2020
  - From October 26, 2020, to June 30, 2021
- For the UK:
  - From March 18, 2020, to September 30, 2021

9.4. Study outcomes

The study outcomes will be:

- The monthly incidence of drug use will be estimated and defined as the number of incident users during the month of interest divided by the person-time in days of the whole database population during that month divided by the number of days in that month.
- The monthly prevalence of drug use will be estimated and defined as the number of prevalent users during the month of interest divided by the person-time in days of the whole database population during that month divided by the number of days in that month.
- The risk of being off treatment during the treatment episode will be estimated as the number of days without treatment (in a gap between consecutive prescriptions) divided by the treatment episode duration in days.

9.5. Data Sources

9.5.1. The Netherlands: PHARMO Database Network

The data source description for CPRD is cited from the book Databases for Pharmacoepidemiological Research [22].

"The PHARMO Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient-level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymisation of the data is performed by STIZON. STIZON is an independent, ISO/IEC 27001 certified foundation which acts as a Trusted Third Party (TTP) between the data sources and the PHARMO Institute."

"All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status (based on zip code), and mortality (only date of death). Other available information depends on the data source. Two types of databases can be distinguished in the PHARMO Database Network. The in-house databases are collected and processed by STIZON. The core partnership databases are collected and processed by other parties."

"Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year."

The PHARMO in-house databases include:

- "The Outpatient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the outpatient pharmacy. Some high-budget impact medications cannot be dispensed by community pharmacies and are dispensed by hospital-based outpatient pharmacies. For a subset of patients, information is available on medication dispensed by these hospital-based outpatient pharmacies. The dispensing records include information on the type of product, date, strength, dosage regimen, quantity, route of administration, prescriber speciality and costs. Drug dispensing data are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Outpatient pharmacy data cover a catchment area representing approximately 25% of the Dutch population."
- The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes but can also be entered as free text. GP data cover a catchment area representing ~20% of the Dutch population.
- The Hospital admissions dataset comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required (i.e. inpatient records). The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Diagnoses are coded according to the WHO International Classification of Diseases, and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures which link to the Dutch Healthcare Authority (NZa) declaration codes and the Dutch Classification of Procedures. Currently, PHARMO has access to data from 1998 onwards and of over 80% of the hospitals."

PHARMO is listed as a data source in the ENCePP resources database (https://www.encepp.eu/encepp/viewResource.htm?id=45066).

9.5.2. The United Kingdom: CPRD

The data source description for PHARMO is cited from the book Databases for Pharmacoepidemiological Research [22].

"CPRD receives all de-identified electronic health records from the patient population of consenting UK general practices, with the exception of individual patients who have opted out of contributing data to CPRD. There are four main primary care patient management software systems in the UK, and CPRD currently receives data from practices using Vision® and EMIS Health® systems. Data from practices using Vision® are curated into the CPRD GOLD database (Herrett et al. 2015), while data from practices using EMIS Health® are curated into the CPRD Aurum database (Wolf et al. 2019)."

"The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in reading Codes. Validation of data with original records (specialist letters) is also available. The dataset is generalisable to the UK population based upon age, sex, socioeconomic class and national geographic coverage when GOLD & Aurum versions are used."

"Patient-level data from consenting GP practices are linked via a trusted third party (TTP) using the NHS number, the exact date of birth, sex and patient residence postcode. CPRD does not receive or hold patient identifiers since they are removed prior to the transfer of data to CPRD to protect patient confidentiality. Personal identifiers are sent separately from GP practices to the TTP to enable linkage. Established linkages include Hospital Episode Statistics (hospitalisation data, including hospital admission and discharge dates, primary diagnosis for the admission using the ICD10 coding system, all clinically recorded data and all procedures performed as well as Maternity, Critical, and Augmented Care Data, but not in-hospital prescriptions) (Herbert et al. 2017), Office for National Statistics Death Registration Data (including date, place and causes of death) (Office for National Statistics 2018b), several measures of area-level deprivation [Index of Multiple Deprivation (Ministry of Housing C& LG 2015) and Townsend scores (Office for National Statistics 2018a)] as proxies of socioeconomic scores, and disease registries including the National Cancer Registration and Analysis Service (Public Health England 2017)."

CPRD is listed as a data source in the ENCePP resources database (https://www.encepp.eu/encepp/viewResource.htm?id=30008).

9.5.3. Lithuania: Electronic health information system (ESPBI-IS)

Lithuanian electronic health system is composed of a central electronic health information system (ESPBI IS) and its subsystems, including the electronic health records subsystem, electronic

prescription subsystem, national medical imaging archive and exchange subsystem. The main use of the ESPBI IS to facilitate the collection of medical information of the patient and sharing it between different healthcare specialists [23].

The electronic prescription subsystem (primary data source for this study) gathers information on electronic prescription data (number, date of discharge, data about the personal health care institution (name of the health care institution, legal entity code, identification code in the Compulsory Health Insurance Information System "Sveidra"), data about the patient (patient name(s), surname(s), date of birth, age, sex, personal code of a resident of the Republic of Lithuania or personal code of a citizen of a foreign country or other identification code, residential address, telephone number, e-mail address. In cases where the patient is treated anonymously, only the patient code is indicated), data about the healthcare professional (name(s), surname(s), press number, professional qualification), the individual's outpatient treatment accounting card or the statistical card of a person treated in an inpatient facility, or the identifier number, code and name of the type of compensation issued by ESPBI IS for the electronic prescription issued during the patient's visit, the effective date of the prescription, the date until which the prescription is valid, the number of days the prescription is valid, the code and name of the disease or other health disorder according to ICD-10-AM, the tags "Compensatory", "First appointment", "Narcotic medicinal product", "Psychotropic medicinal product", "Special appointment", "Named medicinal product", "For long-term treatment", "For continued treatment", number of dispenses, date until which the statement of prescribing the medicinal product is valid, indication that there is patient consent, anatomical-therapeutic-chemical (ATC) classification index level 5 code, if a registered medicinal product is prescribed, name of the active substance, specific trade name, strength, pharmaceutical form, number of dosages of the medicinal product, dosage, package, package size and number of packages [23].

The ESPBI IS contains around 86-99% of prescriptions for medicines covered by the national health insurance issued by any prescriber. It also contains data on 63-74% of hospitalisation episodes and 33-78% of GP or specialist visits, and 100% of all birth and death certificates [24].

9.6. Study size

NL-PHARMO: a total (cumulative) number of persons with actual data is 10.0 million.

UK-CPRD: a total (cumulative) number of persons with actual data is 35.0 million.

LT-ESPBI-IS: covers ~98% of all registered residents in Lithuania, which is ~2.6 million.

9.7. Data management

The data will be analysed separately for each database using the same analytical approaches.

9.8. Data analysis

9.8.1. Missing Data

The absence of relevant information will be viewed as the absence of corresponding events (e.g. prescriptions/dispensings). For numeric variables, the proportion of patients with missing values will be reported.

If information about prescribed/dispensed medicine package size, the number of units, and the prescribed daily dose data is missing, we will impute a duration based on either the most common duration for prescribing the specific medicines in clinical practice in the country or the duration based on the assumption that one defined daily dose (DDD) will be used per day.

9.8.2. Statistical Analysis

All analyses will be stratified by drug group (listed in section 9.3.2.), by database (listed in section 9.4), and by age group (see section 9.2.4.). Patients' characteristics at cohort entry (index date) will be summarised. Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimal and maximal values. Categorical variables will be described by the number and percentage of patients in each category.

An exploratory descriptive analysis will be conducted for each database separately. Baseline characteristics as observed on the treatment initiation date will be summarised for each database. The statistical analyses will be carried out using ARIMA models for interrupted time series analysis [25].

9.8.3. Sensitivity Analysis

The sensitivity analyses provided in Table 1 will be conducted in addition to the primary analyses:

Table 1. Sensitivity analyses

	Main definition	**An alternative definition for sensitivity analysis**
Enrollment in a database before inclusion in the study cohort	12 months	**3 months** **6 months** **24 months**

Prescription incidence rate	Monthly incidence Quarterly incidence	**Biweekly incidence** **Semi-yearly incidence**
Analytical method	ARIMA models	**Join-point regression** **Poisson regression**
Incident user	No prescription or dispensing for the same drug is recorded for 90 days (for antibiotics and ivermectin – 30 days) prior to that prescription/dispensing or estimated treatment episode ended more than 90 days (for antibiotics and ivermectin – 30 days) prior to that prescription/dispensing, whichever comes latest.	- No prescription or dispensing for **the drug of the same chemical subgroup** (based on ATC classification) is recorded for 90 days (for antibiotics and ivermectin – 30 days) prior to that prescription/dispensing or estimated treatment episode ended more than 90 days (for antibiotics and ivermectin –30 days) prior to that prescription/dispensing, whichever comes latest. - No prescription or dispensing for the same drug is recorded for **180 days** (for antibiotics and ivermectin – **60 days**) prior to that prescription/dispensing or estimated treatment episode ended more than **180 days** (for antibiotics and ivermectin – **60 days**) prior to that prescription/dispensing, whichever comes latest.
COVID-19 restriction period	The time when at least one of the restrictions involving mandatory national-level educational facility closing or work closure is implemented fully	The time when at least one of the restrictions involving mandatory national-level educational facility closing or work closure is implemented fully **or partially**

The UK data analysis	The UK as a whole	Separately England, Northern Ireland, Scotland, and Wales

9.9. Quality Control

This study will adhere to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Guidelines for Good Pharmacoepidemiology Practices (GPP) developed by the International Society for Pharmacoepidemiology (ISPE) and Good pharmacovigilance practices (GVP) developed by EMA [26–28].

9.9.1. Quality management

All scripts will be programmed according to agreed coding standards and will be validated by double programming or source code review with the involvement of a second programmer. The newest available version of R and its packages will be used for statistical analyses.

Utrecht University will be responsible for the project management of the study. The Division of Pharmacoepidemiology & Clinical Pharmacology (PECP) at Utrecht University is working according to a quality management system based on ISO 9001 principles and uses a Virtual Desktop Infrastructure (VDI) to ensure secure and safe access to research data.

9.9.2. Data Quality

Project members from the Division of Pharmacoepidemiology & Clinical Pharmacology at Utrecht University will lead and coordinate the data quality checks.

9.10. Limitations of the research methods

The study will use secondary data from two different sources. Since the main purpose of the data sources is not to collect data for research, not all the data might be captured in the most suitable way to assess the objectives of this study.

Data sources used do not record indications for the prescribed/dispensed medications, and the association between the two is made by using a diagnosis code that is proximal to the prescription/dispensing. This might lead to the misclassification of some cases.

The data sources are used to capture data from only a subset of the national populations of the corresponding countries.

10. Protection of human subjects

Data sources used in this study have well-developed mechanisms to ensure that European and local regulations dealing with the ethical use of the data and adequate privacy control are adhered to.

11. Management and reporting of adverse events/adverse reactions

This is a non-interventional study based on secondary use of data, so reporting adverse events (AE) and adverse drug reactions (ADR) on an individual level is not applicable.

12. Plans for disseminating and communicating study results

The study protocol will be uploaded to the EU PAS register prior to data analysis.

Once the study is complete, the final results will be submitted for publication in a peer-reviewed journal and uploaded to the EU PAS register.

The study results also will be used in Tomas Lasys' PhD thesis.

13. References

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Supplements

1. Exposure_code_list.xlsx