# Study Protocol

# P3-C1-022

# DARWIN EU® - Drug Utilisation Study on Antibiotics in the 'Access' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use

19/09/2025

Version 3.0

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| **Study title** | DARWIN EU® - Drug utilisation study on antibiotics in the 'Access' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use |
| **Protocol version** | V3.0 |
| **Date** | 19/09/2025 |
| **EUPAS number** | EUPAS1000000663 |
| **Active substance** | All antibiotics listed under the WHO AWaRe 'Access' category 2023, as outlined in section 8.6.1. |
| **Medicinal product** | n/a |
| **Research question and objectives** | What is the incidence of prescriptions of antibiotics in the 'Access' category from 2012-2024, stratified by demographic characteristics, calendar year/month, and country? Additionally, what are the recorded indications and treatment durations for these prescriptions?<br><br>The specific objectives are:<br><br>1. To investigate the incidence of prescription of individual antibiotics and antibiotics class (from the WHO AWaRe 'Access' category), stratified by age, sex, calendar year/month during the study period 2012-2024.<br>2. To characterise individual antibiotics and antibiotics class (WHO AWaRe 'Access' category 2023) use by duration of use over the study period 2012-2024.<br>3. To characterise individual antibiotic and antibiotics class (WHO AWaRe 'Access' category 2023) use by indication of use stratified by calendar year over the period 2012-2024. |
| **Countries of study** | Croatia, Denmark, Finland, Germany, the Netherlands, Spain |
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# LIST OF ABBREVIATIONS

| Acronyms/term | Description |
|---|---|
| AMR | Antimicrobial Resistance |
| AWaRe | Access, Watch, and Reserve |
| CC | Coordinating centre |
| CDM | Common Data Model |
| CIPH | Croatian Institute of Public Health |
| COPD | Chronic obstructive pulmonary disease |
| DA | Disease Analyzer |
| DARWIN EU® | Data Analysis and Real-World Interrogation Network |
| DK-DHR | Danish Data Health Registries |
| DOI | Declaration of Interests |
| DQD | Data Quality Dashboard |
| DRE | Digital Research Environment |
| DUS | Drug Utilization Study |
| EHR | Electronic Health Records |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FinOMOP-THL | Finish Care Register for Health Care |
| GDPR | General Data Protection Regulation |
| GP | General Practitioner |
| ICD | International Classification of Diseases |
| IP | Inpatient |
| IPCI | Integrated Primary Care Information |
| NAJS | The National Public Health Information System Croatia |
| OHDSI | Observational Health Data Sciences and Informatics |
| OMOP | Observational Medical Outcomes Partnership |
| OP | Outpatient |
| RxNorm | Medical prescription normalized |
| SD | Standard Deviation |
| SIDIAP | The Information System for Research in Primary Care |
| SNOMED | Systematized Nomenclature of Medicine |
| WHO | World Health Organisation |
| WONCA | World Organization of Family Doctor |

# 1. TITLE

DARWIN EU® - Drug utilisation study on antibiotics in the 'Access' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use

# 2. DESCRIPTION OF THE STUDY TEAM

| Study team role | Names | Organisation |
|---|---|---|
| Principal Investigators | Marzyeh Amini<br>Katia Verhamme<br>Nicholas Hunt | Erasmus MC |
| Data Scientists | Ger Inberg<br>Ioanna Nika | Erasmus MC |
| Study Manager | Natasha Yefimenko | Erasmus MC |
| **Data Partner*** | **Names** | **Organisation** |
| DK-DHR | Claus Møldrup<br>Elvira Bräuner<br>Susanne Bruun | Danish Medicines Agency |
| FinOMOP-THL | Tiina Wahlfors<br>Gustav Klingstedt<br>Toni Lehtonen | Finnish Institute for Health and Welfare |
| IPCI | Katia Verhamme<br>Ger Inberg | Erasmus MC |
| IQVIA DA Germany | Dina Vojinovic<br>Akram Sharim Mendez Rangel<br>Ellen Gerritsen<br>Gargi Jadhav<br>Hugo Vernooij<br>Isabella Kaczmarczyk | IQVIA |
| NAJS | Antea Jezidžić<br>Marko Čavlina<br>Karlo Pintaric<br>Anamaria Jurcevic | Croatian Institute of Public Health |

| | | |
|---|---|---|
| | Jakov Vukovic | |
| SIDIAP | Agustina Giuliodori Picco<br>Irene López Sánchez<br>Elena Roel Herranz<br>Talita Duarte Salles | IDIAP JGol |

*Data partners' role is to execute code at their data source, review and approve their results. They do not have an investigator role.

# 3. ABSTRACT

**Title**

DARWIN EU® – Drug utilisation study on antibiotics in the 'Access' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use

**Rationale and background**

The WHO 2023 AWaRe classification (who.int) of antibiotics for evaluation and monitoring of use classifies 258 antibiotics into 3 categories (Access/Watch/Reserve) according to their impact on antimicrobial resistance.

The 'Access' category includes antibiotics that are recommended as first- or second-line treatments for a wide range of common infectious diseases. These antibiotics are generally active against a broad spectrum of commonly encountered, susceptible pathogens and have a relatively lower risk of promoting antimicrobial resistance compared to agents in other categories. The WHO emphasizes that 'Access' antibiotics should be widely available, affordable, and of assured quality across all healthcare settings to ensure equitable treatment, especially in low- and middle-income countries. As of the 2023 update, the 'Access' group includes 84 antibiotics, such as amoxicillin and doxycycline, which are used to treat high-burden infections like pneumonia and urinary tract infections.(1, 2) Promoting the use of 'Access' antibiotics for appropriate indications is a key component of global antimicrobial stewardship strategies aimed at reducing the need for broader-spectrum agents and mitigating the spread of resistance.
The DARWIN EU® P1-C1-003 study focused on the Watch category but there is now interest in including also the other category ('Access') to characterise the use of most antibiotics, and increased focus on the indication for use.

This study will improve the understanding of the use of antibiotics in routine health care delivery, including indication, treatment duration, and trends over time. The results will contribute to the EU efforts to monitor use of antibiotics as part of the global fight against antimicrobial resistance.

**Research question and objectives**

Research question

What is the incidence of prescriptions of antibiotics in the 'Access' category from 2012 to 2024, stratified by demographic characteristics, calendar year/month, and country? Additionally, what are the recorded indications and treatment durations for these prescriptions?

Objectives

1. To investigate the incidence of prescription of individual antibiotics and antibiotics class (from the WHO AWaRe 'Access' category), stratified by age, sex, calendar year/month during the study period 2012-2024.
2. To characterise individual antibiotics and antibiotics class (WHO AWaRe 'Access' category 2023) use by duration of use over the study period 2012-2024.
3. To characterise individual antibiotic and antibiotics class (WHO AWaRe 'Access' category 2023) use by indication of use stratified by calendar year over the period 2012-2024.

**Methods**

Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on 'Access' category antibiotics)

- New drug user cohort study (Objectives 2 and 3, Patient-level drug utilisation analysis with regard to duration and indication of antibiotics use)

Population

*Objective 1*: All individuals present in the database in the period between 01/01/2012 and 31/12/2024 will be included in the analysis after 365 days of database history.

*Objectives 2 and 3:* All new users of antibiotics (i.e. no use of the antibiotic of interest in the preceding 30 days) in the period between 01/01/2012 and 31/12/2024, with at least 365 days of visibility prior to the date of their first antibiotic prescription.

Study period

Study period will start from 2012 until the end of available data. In the NAJS data source, accurate data will be available from 2017 on.

Variables

*Exposures*

All antibiotics from the WHO AWaRe 'Access' category.

*Outcome*

n/a

*Relevant covariates*

Age groups, sex, calendar year/month, and predefined conditions of interest derived from WHO AWaRe handbook.

Data source

1. Danish Data Health Registries (DK-DHR), Denmark
2. Finnish Care Register for Health Care (FinOMOP-THL), Finland
3. The Integrated Primary Care Information (IPCI), the Netherlands
4. IQVIA Disease Analyser (DA) Germany, Germany
5. National Public Health Information System (NAJS), Croatia
6. Information System for Research in Primary Care (SIDIAP), Spain

Sample size

No sample size has been calculated as this is an exploratory study which will not test a specific hypothesis.

Statistical analysis

*Objective 1*: Yearly and monthly incidence rates of individual antibiotics and antibiotics class prescriptions per 100,000 person-years (PYs) will be estimated. Overall incidence rates will be reported as well as stratified by age, sex, calendar year/month, and country/database. Incidence rates will be reported together with 95% Poisson confidence intervals.

*Objectives 2 and 3*: The indication of use will be assessed and reported as the proportion of individuals with a disease code of interest at index date and within predefined windows (within +/-7 days, -30 - +7 days, and -60 - +7 days around the index date). Index date will be the date of each prescription of the specific antibiotic for each person. Cumulative treatment duration will be estimated and the minimum, p25,

median, p75, and maximum will be provided. Results will be further stratified by calendar year (2012-2024) and by antibiotics class.

The statistical analyses will be performed based on OMOP-CDM mapped data using "*IncidencePrevalence*" and "*DrugUtilization*" R packages. A minimum cell counts of 5 will be used when reporting results, with any smaller count reported as "<5".

# 4. AMENDMENTS AND UPDATES

None.

# 5. MILESTONES

| Study milestones and deliverables | Planned dates |
|---|---|
| Final study protocol | To be confirmed by EMA |
| Creation of analytical code | 01st July 2025 |
| Execution of analytical code on the data | 08th July 2025 |
| Draft study report | 29th September 2025 |
| Final study report | To be confirmed by EMA |

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources.

# 6. RATIONALE AND BACKGROUND

Bacterial infections are a major cause of morbidity and mortality worldwide.(3) Antibiotics have played a pivotal role in improving global health outcomes. Alongside advancements in nutrition, clean water access, sanitation, and vaccination programs, they have significantly contributed to the reduction of under-five mortality rates and the increase in life expectancy over the past decades. In 1950, the global under-five mortality rate was approximately 216 deaths per 1,000 live births. By 2022, this rate had declined to 37 deaths per 1,000 live births, marking a 59% reduction since 1990. Concurrently, global life expectancy has seen a substantial rise. In 1950, the average life expectancy at birth was around 45.7 to 48 years. By 2023, this figure had increased to approximately 73.16 years. These improvements underscore the critical impact of antibiotics and other public health interventions in enhancing child survival and extending life expectancy worldwide.(4-7)

Antibiotics play a crucial role in the treatment of infections caused by bacteria but one of the greatest concerns is the risk of resistance evoked through the inappropriate use of antibiotics with regard to indication and duration of use.(8) To improve the appropriate use of antibiotics, Antimicrobial Stewardship Programs (ASPs) have been installed with the aim in promoting appropriate antibiotic use by monitoring prescriptions and enforcing adherence to clinical guidelines. Recent studies show ASPs reduce total antibiotic use by over 19% and help lower rates of resistant infections.(9-11)

The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support ASPs efforts at local, national, and global levels. Antibiotics are classified into three groups, 'Access', 'Watch' and 'Reserve', taking into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance, to emphasize the importance of their appropriate use. (12)

The 'Access' antibiotic category of the AWaRe program includes antibiotics with a lower resistance potential, recommended as first- or second-line treatments for common infections. These antibiotics are prioritized for broad accessibility and appropriate use to support antimicrobial stewardship and reduce reliance on higher-risk antibiotics. The WHO 13th General Programme of Work (2019–2023) set a target for at least 60% of total antibiotic consumption to come from 'Access' antibiotics, making this category a key

tool for monitoring antibiotic use and evaluating stewardship policies to combat antimicrobial resistance.(13)

This study will improve our understanding of the use of antibiotics in the 'Access' category in routine health care delivery, including indication, treatment duration, and trends over time. The results will contribute to the EU efforts to monitor use of antibiotics as part of the global fight against antimicrobial resistance.

# 7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the incidence of prescriptions of antibiotics in the 'Access' category from 2012 to 2024, stratified by demographic characteristics and calendar year/month? Additionally, what are the recorded indications and treatment durations for these prescriptions?

The proposed objectives to be achieved in the study are described in **Table 1**.

**Table 1.** Primary and secondary objective.

**A. Primary objective.**

| | |
|---|---|
| **Objective(s):** | To investigate the incidence of prescription of individual antibiotics and antibiotics class (from the WHO AWaRe 'Access' category), stratified by age, sex, calendar year/month during the study period 2012-2024. |
| **Hypothesis:** | n/a |
| **Population *(mention key inclusion-exclusion criteria):*** | The study population will include all individuals present in the database in the period 2012 to 2024, with at least 365 days of data availability before the day they become eligible for study inclusion.<br>Additional eligibility criteria will be applied for the calculation of incidence rates where observation time of the respective use of the antibiotic of interest is excluded during use and 30 days afterwards. |
| **Exposures:** | Antibiotics from the WHO AWaRe 'Access' category 2023 |
| **Comparator:** | n/a |
| **Outcome:** | n/a |
| **Time *(when follow up begins and ends):*** | Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year/month between 2012 to 2024 for the calculation of yearly/monthly incidence rates.<br>End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2024). |
| **Setting:** | Inpatient and/or outpatient setting using data from the following data sources: DK-DHR (Denmark), FinOMOP-THL (Finland), IPCI (Netherlands), IQVIA DA (Germany), NAJS (Croatia), SIDIAP (Spain) |
| **Main measure of effect:** | Incidence rates of antibiotic use with 95% confidence intervals |

**A. Secondary objective 1.**

| | |
|---|---|
| **Objectives:** | To characterise individual antibiotics and antibiotics class (WHO AWaRe 'Access' category 2023) use by duration of use over the study period 2012-2024. |
| **Hypothesis:** | n/a |
| **Population *(mention key inclusion-exclusion criteria):*** | The study cohort will comprise all individuals present in the data source in the period 2012-2024 (or the latest available data), with at least 365 days of data availability before the day they become eligible for study inclusion and who had received at least one prescription of one of the antibiotics of interest after not using the specific antibiotic in the preceding 30 days. |
| **Exposure:** | Antibiotics from the WHO AWaRe 'Access' category 2023 |
| **Comparator:** | n/a |
| **Outcome:** | n/a |
| **Time *(when follow up begins and ends):*** | Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2024.<br>End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2024) |
| **Setting:** | Outpatient and/or inpatient setting using data from the following data sources: DK-DHR (Denmark), FinOMOP-THL (Finland), IPCI (Netherlands), IQVIA DA (Germany), NAJS (Croatia), SIDIAP (Spain) |
| **Main measure of effect:** | Duration of antibiotic use expressed as minimum, p25, median, p75, and maximum. |

**B. Secondary objective 2.**

| | |
|---|---|
| **Objectives:** | To characterise individual antibiotic and antibiotics class (WHO AWaRe 'Access' category 2023) use by indication of use, stratified by calendar year over the period 2012-2024. |
| **Hypothesis:** | n/a |
| **Population *(mention key inclusion-exclusion criteria):*** | The study cohort will comprise all individuals present in the database in the period 2012-2024 (or the latest available data), with at least 365 days of data availability before the day they become eligible for study inclusion and who had received at least one prescription of one of the antibiotics of interest after not using the specific antibiotic in the preceding 30 days. |
| **Exposure:** | Antibiotics from the WHO AWaRe 'Access' category 2023 |
| **Comparator:** | n/a |
| **Outcome:** | n/a |

| | |
|---|---|
| **Time *(when follow up begins and ends):*** | Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2024.<br><br>End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2024). |
| **Setting:** | Outpatient and/or inpatient setting using data from the following data sources: DK-DHR (Denmark), FinOMOP-THL (Finland), IPCI (Netherlands), IQVIA DA (Germany), NAJS (Croatia), SIDIAP (Spain) |
| **Main measure of effect:** | Proportion (percentage) of patients with one of the defined indications of use at time of antibiotic prescribing/dispensing and over time between 2012 and 2024. |

# 8. RESEARCH METHODS

## 8.1. Study type and study design

This will be a retrospective cohort study per DARWIN EU® Catalogue of Standard Data Analyses using routinely collected health data from 6 European countries.(14) The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the incidence of the WHO AWaRe 'Access' category antibiotics (by individual antibiotic and by antibiotics class).
2. A new drug user cohort will be used to address objectives 2 and 3; to characterise patient-level WHO AWaRe 'Access' category antibiotics utilisation in terms of duration and indication of use.

A graphical description of the study design is shown in the **Figure 1**.

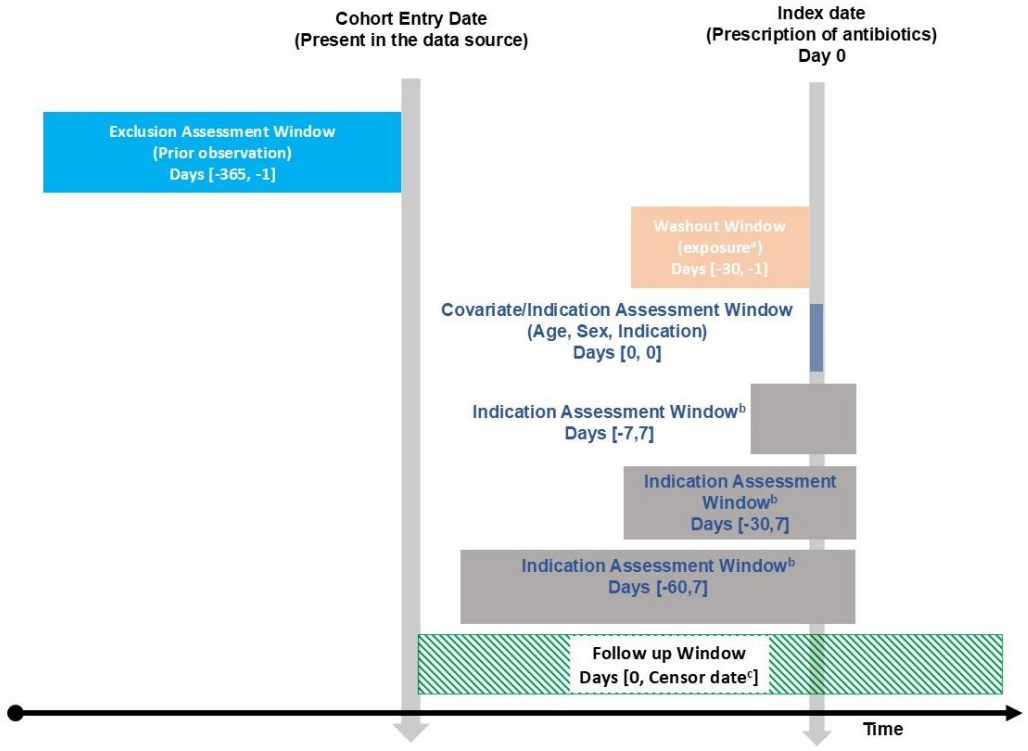


**Figure 1.** A graphical depiction of the study design

a. Antibiotic (ingredient) of interest
b. Sensitivity analysis to assess indication of use in a wider window around the index date
c. Earliest date of: Loss to follow-up, death, end of the observation period or data availability

## 8.2. Study setting and data sources

This study will be conducted using routinely collected data from 6 primary/secondary care databases in the DARWIN EU® network of data partners from 6 European countries.

Data sources

1. Danish Data Health Registries (DK-DHR), Denmark
2. Finnish Care Register for Health Care (FinOMOP-THL), Finland
3. The Integrated Primary Care Information (IPCI), the Netherlands
4. IQVIA Disease Analyser (DA) Germany, Germany
5. National Public Health Information System (NAJS), Croatia
6. Information System for Research in Primary Care (SIDIAP), Spain

Data Selection

These databases fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for population level drug utilization studies while covering different regions of Europe. Detailed information on the selected data sources is described in **Table 2.**

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To

further ensure data quality, we utilised the Achilles tool,(15) which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, data density. Data density includes information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source), 2) measurement value distribution (i.e. min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of databases was based on the availability of data on the selected antibiotics of interest to perform the described analyses. In addition, the databases were chosen considering their ability to support timely IRB approvals, thus ensuring alignment with the timeline established by stakeholders for the conduct of this study.

The DARWIN EU® portal as well as information from the onboarding documents were used to assess whether databases have information on use of treatments and indications of interest. Data within the DARWIN EU® portal is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time covered by each released database, as this can vary across different domains. To facilitate this, the C*DMOnboarding* (and *Achilles*) packages (15) contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows to get insights when data collection started, when new sources of data were added and until when data was included. In addition, at time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *CohortDiagnostics* (16) and *DrugExposureDiagnostics* (17), have been developed. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts, and index event misclassification. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records. Upon finalisation of the study protocol and creation of the disease and drug cohorts of interest by DARWIN EU Coordination Centre, these packages will be executed in each data sources by each data partners.

**Table 2.** Description of the selected data sources.

| Country | Name of Database | Justification for Inclusion | Health Care setting | Objectives | Type of Data | Number of active persons* | Feasibility counts of disease (if relevant) | The data lock date of the most recent update |
|---|---|---|---|---|---|---|---|---|
| Denmark | DK-DHR | The data source includes inpatient hospital care and secondary outpatient care where adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of DK-DHR contributes to geographical diversity of data sources included with adequate data availability over the study period. | Inpatient hospital care and secondary outpatient care | 1, 2, and 3 | EHRs, registries, others | 5.98M | n/a | 2025-04-10 |
| Finland | FinOMOP-THL | The data source includes primary care, outpatient specialist care, and inpatient care where adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of FinOMOP-THL contributes to geographical diversity of data sources included with adequate data availability over the study period. | Primary care, outpatient specialist care, and inpatient care | 1 and 3** | EHR and registries | 5.70M | n/a | 2024-10-01 |

| Country | Name of Database | Justification for Inclusion | Health Care setting | Objectives | Type of Data | Number of active persons* | Feasibility counts of disease (if relevant) | The data lock date of the most recent update |
|---|---|---|---|---|---|---|---|---|
| The Netherlands | IPCI | The data source includes primary care where adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of IPCI contributes to geographical diversity of data sources included with adequate data availability over the study period. | Primary Care | 1, 2, and 3 | EHR | 1.25M | n/a | 2025-04-16 |
| Germany | IQVIA Germany | The data source includes primary care and outpatient specialist care where adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of IQVIA Germany contributes to geographical diversity of data sources included with adequate data availability over the study period. | Primary care and outpatient specialist care | 1, 2, and 3 | EHR | 4.56M | n/a | 2025-04-10 |
| Croatia | NAJS | The data source includes primary care, outpatient specialist care, and inpatient care where | Primary care, outpatient specialist | 1, 2, and 3 | Registries | 4.22M[#] | n/a | 2025-02-08 |

| Country | Name of Database | Justification for Inclusion | Health Care setting | Objectives | Type of Data | Number of active persons* | Feasibility counts of disease (if relevant) | The data lock date of the most recent update |
|---|---|---|---|---|---|---|---|---|
| | | adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of NAJS contributes to geographical diversity of data sources included with adequate data availability over the study period. | care, and inpatient care | | | | | |
| Spain | SIDIAP | The data source includes primary care where adequate number of patients exposed to the WHO AWaRe 'Access' category antibiotics and predefined medical conditions can be recorded.<br>Use of SIDIAP contributes to geographical diversity of data sources included with adequate data availability over the study period. | Primary care | 1, 2, and 3 | EHR | 5.95M | n/a | 2023-08-30 |

* Active persons are defined as the maximum number of persons in an observation period of each data source, in the last 6 months.

# The person table in the NAJS data source also included both deceased individuals and those who were previously insured, meaning the number of subjects exceeds the number of currently living individuals.

** In the current release of the OMOP CDM version of the FinOMOP THL database, drug exposures are based solely on prescription records, and the end dates for these exposures have been entirely imputed. Thus, the current exposure durations are not indicative of the actual period during which the patient was expected to be exposed to the drug.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care; IPCI=The Integrated Primary Care Information; DA=Disease Analyser; NAJS=National Public Health Information System; SIDIAP=Information System for Research in Primary Care; EHR=Electronic Health Records

Danish Data Health Registries (DK-DHR), Denmark

Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Laboratory Database including Coronavirus disease 2019 test results) and The Vaccination Registry (including COVID-19 vaccinations).

Finnish Care Register for Health Care (FinOMOP-THL), Finland

The FinOMOP THL database covers both public and private, primary, and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care (fi:Hoitoilmoitusrekisteri, HILMO). It is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998 the register has covered both public outpatient and inpatient specialized care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, and positive COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM is currently produced from the above-mentioned and limited to observation periods commencing after 1.1.2011. The National Population registry is also used as a source for the CDM database. The National Population registry data forms the basis for forming the patient population. This ensures up-to-date location (municipality of residence) of patients as well as complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.(18) IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Centre in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors, and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented and IPCI has proved valuable for epidemiological studies.(19-23) In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, proportion of patients with blood pressure measurement, etc.(18) Based on this information, two quality scores have been created. Practices with low scores have been excluded.

IQVIA Disease Analyser (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialized and general primary practices (GP) in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape.(24, 25) The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country.(24, 25) Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records.(25) While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore information on mortality is incomplete. Routine updates are conducted at regular intervals. The quality of data is assessed based on several criteria including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions). IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies as previously demonstrated.(25-27)

National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse, and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2017.

Information System for Research in Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.(28) It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented and SIDIAP has proved valuable for epidemiological studies.(26, 29-36) In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values) and consistency using visualization tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

## 8.3. Study period

The study period will be from the 1st of January 2012 until the earliest of 31st December 2024 or the respective latest date of data lock of the respective databases. Follow-up will start from the date they have reached at least 365 days of data availability (except for children <1 year during the study period where follow-up starts at time of registration in the database). It should be noted that in the NAJS data source, the availability of accurate data starts from 1st January 2017.

## 8.4. Follow-up

For objective 1, follow-up will start on the first date, within the study period, when an individual becomes eligible to enter the study (i.e., index date as defined in **Table 3**), and will continue until the earliest of the following: loss to follow-up, death, end of observation period (the most recent data available) in the database.

An example of entry and exit into the denominator population is shown in **Figure 2**. In this example, person ID 1 has already sufficient prior history before the study start date and observation period ends after the study end date, so will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

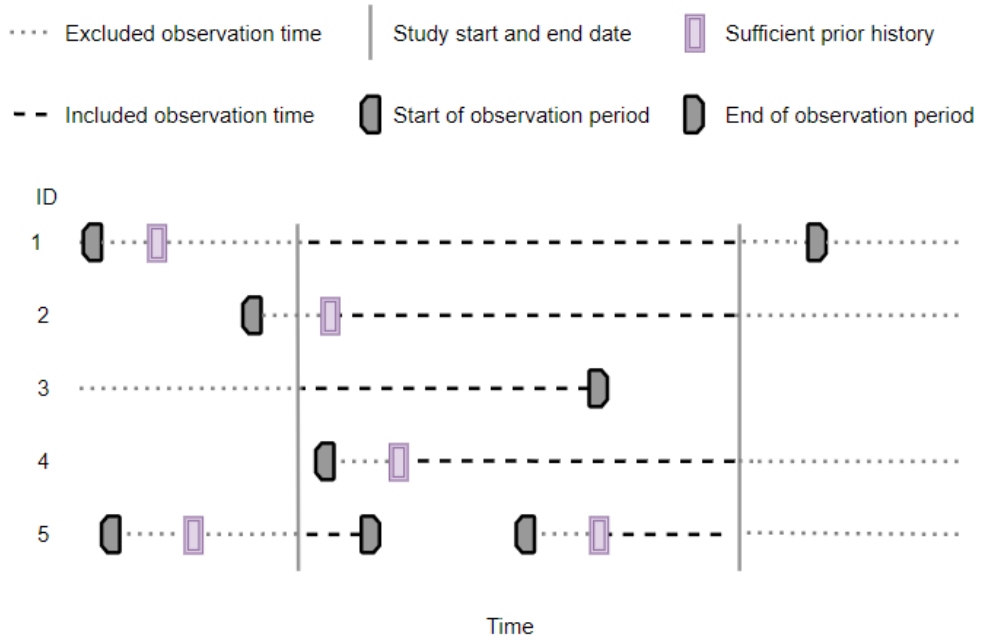


**Figure 2.** Included observation time for the denominator population.

Operational definition of the index dates for each of the cohorts mentioned above and other primary time anchors are described in **Table 3**.

**Table 3.** Operational definition of time 0 (index date).

| Study population name(s) | Time Anchor Description (time 0 or index date) | Number of entries | Type of entry | Washout window | Care Setting[1] | Code Type[2] | Diagnosis position | Incident with respect to… | Measurement characteristics/validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Antibiotic drug use | Individuals with an antibiotic drug prescription present in the data source during the study period (2012-2024) and with at least 1 year of valid data source history (except for hospital data sources and children < 1 year during study period) | Multiple | Incident | [-30, -1] | IP and OP | n/a | n/a | Specific antibiotics | n/a | n/a |

[1] IP = inpatient, OP = outpatient, n/a = not applicable

[2] The type(s) of clinical codes that are used to define the time 0 (or another primary anchor) criterion

## 8.5. Inclusion and exclusion criteria

The study domain includes all persons present in the data sources in the study period: 01/01/2012 to 31/12/2024 (or the latest available date) with at least 365 days observation time (except for children <1 year). This will be used as the denominator population for calculating incidence rates.

The study population for the numerator (incident antibiotic drug use) and for the characterisation population will be defined as follows:

Inclusion criteria

- Individuals with antibiotic prescriptions issued within the study period: 01/01/2012 to 31/12/2024 (or the latest available date).

Exclusion criteria

- Individuals will be excluded if they have used the same antibiotic within the previous 30 days
- Individuals will be excluded if they have less than 365 days of prior data availability (except for children under 1 year old).

Operational definition of the inclusion and exclusion criteria for each of the cohorts mentioned above are described in **Table 4** and **Table 5**, respectively.

**Table 4.** Operational definitions of inclusion criteria.

| Criterion | Details | Order of application * | Assessment window | Care Settings[1] | Code Type | Diagnosis position[2] | Applied to study populations | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|---|
| Observation period in the database during the study period 2012-2024 (or the latest available) | All individuals present in the study period | After study start date | n/a | IP, OP, OT | n/a | n/a | All individuals within the selected databases | n/a | n/a |
| Antibiotic prescription or dispensing in the study period 2012-2024 (or the latest available) | All prescriptions or dispensing in the study period with a 30-day wash out period. Used for incident drug user population (characterisation and incidence rates) | After study start date | n/a | IP, OP, OT | RxNorm | n/a | All individuals within the selected databases | n/a | n/a |

[1] OP = outpatient, IP = inpatient, OT = other, n/a = not applicable

[2] The type(s) of clinical codes that are used to define the inclusion criteria.

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting “before” means that all possible study entry dates are identified, and then one or more is chosen. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient does not meet the criterion, then the patient drops out.

**Table 5.** Operational definitions of exclusion criteria.

| Criterion | Details | Order of application | Assessment window | Care Settings[1] | Code Type[2] | Diagnosis position | Applied to study populations | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|---|
| Observation | Less than 365 days of observation prior to the index date (except for children <1 year and for patients from hospitals data sources) | After study start date | [-365, -1] | OP, IP, and OT | n/a | n/a | All cohorts | n/a | n/a |
| Previous history of antibiotics uses | Recorded history of antibiotics use in the 30 days prior to the index-date | Before index date | [-30, -1] | IP, OP, and OT | RxNorm | n/a | All cohorts | n/a | n/a |

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

[2] The type(s) of clinical codes that are used to define the exclusion criteria.

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting “before” means that all possible study entry dates are identified, and then one or more is chosen. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient does not meet the criterion, then the patient drops out.

## 8.6. Variables

### 8.6.1. Exposures

For this study, the exposure of interest is use (during study period) of individual antibiotics and antibiotics class from the 'Access' category of the WHO 2023 AWaRe classification of antibiotics (who.int) (**Table 6**). The 'Access' category represents antibiotics with a lower resistance potential that are essential for treating common infections, ensuring broad availability and appropriate use to minimize the development of antimicrobial resistance.

**Table 6.** List of WHO 2023 AWaRe 'Access' category as exposures of interest.

| Antibiotics of Reserve category | Class | ATC code |
|---|---|---|
| Amikacin | Aminoglycosides | J01GB06 |
| Amoxicillin | Penicillins | J01CA04 |
| Amoxicillin/clavulanic acid | Beta-lactam/beta-lactamase-inhibitor | J01CR02 |
| Ampicillin | Penicillins | J01CA01 |
| Ampicillin/sulbactam | Beta-lactam/beta-lactamase-inhibitor | J01CR01 |
| Azidocillin | Penicillins | J01CE04 |
| Bacampicillin | Penicillins | J01CA06 |
| Benzathine-benzylpenicillin | Penicillins | J01CE08 |
| Benzylpenicillin | Penicillins | J01CE01 |
| Brodimoprim | Trimethoprim-derivatives | J01EA02 |
| Cefacetrile | First-generation-cephalosporins | J01DB10 |
| Cefadroxil | First-generation-cephalosporins | J01DB05 |
| Cefalexin | First-generation-cephalosporins | J01DB01 |
| Cefaloridine | First-generation-cephalosporins | J01DB02 |
| Cefalotin | First-generation-cephalosporins | J01DB03 |
| Cefapirin | First-generation-cephalosporins | J01DB08 |
| Cefatrizine | First-generation-cephalosporins | J01DB07 |
| Cefazedone | First-generation-cephalosporins | J01DB06 |
| Cefazolin | First-generation-cephalosporins | J01DB04 |
| Cefradine | First-generation-cephalosporins | J01DB09 |
| Cefroxadine | First-generation-cephalosporins | J01DB11 |
| Ceftezole | First-generation-cephalosporins | J01DB12 |
| Chloramphenicol | Amphenicols | J01BA01 |
| Clindamycin | Lincosamides | J01FF01 |
| Clometocillin | Penicillins | J01CE07 |
| Cloxacillin | Penicillins | J01CF02 |
| Dicloxacillin | Penicillins | J01CF01 |
| Doxycycline | Tetracyclines | J01AA02 |
| Epicillin | Penicillins | J01CA07 |
| Flucloxacillin | Penicillins | J01CF05 |
| Furazidin | Nitrofuran derivatives | J01XE03 |
| Gentamicin | Aminoglycosides | J01GB03 |
| Hetacillin | Penicillins | J01CA18 |

| | | |
|---|---|---|
| Mecillinam | Penicillins | J01CA11 |
| Metampicillin | Penicillins | J01CA14 |
| Meticillin | Penicillins | J01CF03 |
| Metronidazole_IV | Imidazoles | J01XD01 |
| Metronidazole_oral | Imidazoles | P01AB01 |
| Nafcillin | Penicillins | J01CF06 |
| Nifurtoinol | Nitrofuran derivatives | J01XE02 |
| Nitrofurantoin | Nitrofuran-derivatives | J01XE01 |
| Ornidazole_IV | Imidazoles | J01XD03 |
| Ornidazole_oral | Imidazoles | P01AB03 |
| Oxacillin | Penicillins | J01CF04 |
| Penamecillin | Penicillins | J01CE06 |
| Phenoxymethylpenicillin | Penicillins | J01CE02 |
| Pivampicillin | Penicillins | J01CA02 |
| Pivmecillinam | Penicillins | J01CA08 |
| Procaine-benzylpenicillin | Penicillins | J01CE09 |
| Propicillin | Penicillins | J01CE03 |
| Secnidazole | Imidazoles | P01AB07 |
| Spectinomycin | Aminocyclitols | J01XX04 |
| Sulbactam | Beta-lactamase-inhibitors | J01CG01 |
| Sulfadiazine | Sulfonamides | J01EC02 |
| Sulfadiazine/tetroxoprim | Sulfonamide-trimethoprim-combinations | J01EE06 |
| Sulfadiazine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE02 |
| Sulfadimethoxine | Sulfonamides | J01ED01 |
| Sulfadimidine | Sulfonamides | J01EB03 |
| Sulfadimidine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE05 |
| Sulfafurazole | Sulfonamides | J01EB05 |
| Sulfaisodimidine | Sulfonamides | J01EB01 |
| Sulfalene | Sulfonamides | J01ED02 |
| Sulfamazone | Sulfonamides | J01ED09 |
| Sulfamerazine | Sulfonamides | J01ED07 |
| Sulfamerazine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE07 |
| Sulfamethizole | Sulfonamides | J01EB02 |
| Sulfamethoxazole | Sulfonamides | J01EC01 |
| Sulfamethoxazole/trimethopr | Sulfonamide-trimethoprim-combinations | J01EE01 |
| Sulfamethoxypyridazine | Sulfonamides | J01ED05 |
| Sulfametomidine | Sulfonamides | J01ED03 |
| Sulfametoxydiazine | Sulfonamides | J01ED04 |
| Sulfametrole/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE03 |
| Sulfamoxole | Sulfonamides | J01EC03 |
| Sulfamoxole/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE04 |
| Sulfanilamide | Sulfonamides | J01EB06 |
| Sulfaperin | Sulfonamides | J01ED06 |
| Sulfaphenazole | Sulfonamides | J01ED08 |
| Sulfapyridine | Sulfonamides | J01EB04 |

| | | |
|---|---|---|
| Sulfathiazole | Sulfonamides | J01EB07 |
| Sulfathiourea | Sulfonamides | J01EB08 |
| Sultamicillin | Beta-lactam/beta-lactamase-inhibitor | J01CR04 |
| Talampicillin | Penicillins | J01CA15 |
| Tetracycline | Tetracyclines | J01AA07 |
| Thiamphenicol | Amphenicols | J01BA02 |
| Tinidazole_IV | Imidazoles | J01XD02 |
| Tinidazole_oral | Imidazoles | P01AB02 |
| Trimethoprim | Trimethoprim-derivatives | J01EA01 |

Operational definition of the exposures is described in **Table 7**. Non-systemic antibiotics will be excluded.

A list of exposure concept IDs (with respective ATC code and concept name) can be seen in **Appendix I, Table S1**.

### 8.6.2. Outcomes

None.

**Table 7.** Operational definitions of exposure.

| Exposure group name(s) | Details | Washout window | Assessment Window | Care Setting[1] | Code Type | Diagnosis position[2] | Applied to study populations | Incident with respect to… | Measurement characteristics/ validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Antibiotics from the 'Access' category of The WHO 2023 AWaRe classification | Preliminary code lists provided in Appendix I, Table S1 | [-30, -1] | Calendar year/month | IP, OP, OT | RxNorm | n/a | All individuals present in the database during the study period | Previous antibiotic use (of the antibiotic of interest) | n/a | n/a |

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### *8.6.3.* Other covariates, including confounders, effect modifiers, and other variables

*Covariates for stratification in objective 1*

- Age at index date will be according to the following categories: 0–<1, 1–<2, 2–<12, 12–<18, 18–<46, 46–<70, >=70.
- Sex (male/female)
- Calendar year/month

*Covariates for objectives 2 and 3*

- Calendar year
- The following conditions will be of interest (i.e., indication of use) based on WHO AWaRe handbook:
    - Eye infections
        - Conjunctivitis
        - Trachoma
        - Endophthalmitis
        - Blepharitis
    - Oral and dental infections
        - Dental abscess
        - Periodontal disease
        - Oral herps simplex infection
    - Pharyngitis
        - Acute tonsillitis/tonsillitis
        - Acute pharyngitis
        - Strep throat
    - Otitis media
    - Sinusitis
        - Acute sinusitis
        - Chronic sinusitis
    - Bronchitis
        - Acute bronchitis
        - Chronic bronchitis
    - Pneumonia
        - Typical pneumonia
        - Atypical pneumonia

- Viral pneumonia

- Chronic obstructive pulmonary disease (COPD)/exacerbation of COPD
  - COPD
  - Exacerbation of COPD
- Asthma/ exacerbation of Asthma
- Endocarditis
- Acute infectious diarrhoea/gastroenteritis
  - Viral gastroenteritis
  - Bacterial gastroenteritis
  - Clostridium difficile infection
- Enteric fever
- Intra-abdominal infections (other than acute infectious diarrhoea/gastroenteritis)
  - Hepatic abscess
  - Peritonitis/intra-abdominal abscess
  - Diverticulitis
  - Cholangitis/Cholecystitis
  - Acute appendicitis
  - Pancreatitis
- Urinary tract infections (UTI)
  - Upper UTI (including upper UTI, pyelonephritis, renal/ perinephric abscess)
  - Lower UTI (including lower UTI, cystitis, urethritis)
- Other genito-urinary infection
  - Prostatitis
  - Epididymo-orchitis
  - Pelvic inflammatory disease
- Sexually transmitted infections
  - Chlamydial urogenital infection
  - Syphilis
  - Trichomoniasis
  - Gonorrhea
- Meningitis and encephalitis
  - Bacterial meningitis
  - Other meningitis

- Encephalitis

- Sepsis or septic shock
- Febrile neutropenia
- Osteomyelitis
- Septic arthritis
- Skin and soft tissue infections
  - Cellulitis
  - Impetigo
  - Erysipelas
  - Wound- and bite-related infections
  - Skin ulcer/diabetic foot
- Localized acute bacterial lymphadenitis
- Surgical prophylaxis
- Other conditions: If there is a record of any condition other than those mentioned above, the individual will be considered as having another indication.

Conditions will be considered as indication for individual antibiotics and antibiotics class use from WHO AWaRe 'Access' category, at index date (i.e. date of each prescribing of antibiotics during the study period) and within +/-7 days, -30 – +7 days, and -60 – +7 days of the index date as sensitivity analysis. These indications will be identified based on the presence of SNOMED disease codes.

List of codes for identifying the conditions of interest are described in **Appendix I, Table S2.**

The operational definitions of the covariates are described in the **Table 8**.

**Table 8.** Operational definitions of covariates.

| Characteristic | Details | Type of variable | Assessment window | Care Settings[1] | Code Type | Diagnosis Position | Applied to study populations | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|---|
| Demographics | Age and sex at index date | Numeric continuous and binary | At index date | IP, OP, and OT | n/a | n/a | All cohorts | n/a | n/a |
| Calendar | Calendar year/month | Numeric | At index date | IP, OP, and OT | n/a | n/a | Individuals with incidence use of antibiotics during the study period | n/a | n/a |
| Indication of Use | Diagnosis records of conditions of interest related to use of antibiotics | Binary | At index date and as sensitivity analyses in windows around index date: [-7, 7], [-30, 7], and [-60,7] | IP, OP, and OT | SNOMED | n/a | Individuals with incidence use of antibiotics during the study period | n/a | n/a |

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

## 8.7. Study size

No sample size has been calculated as this is an exploratory study which will not test a specific hypothesis. In addition, we will use already collected available data to estimate the incidence rates of antibiotic use, explore the duration of antibiotic treatment, and assess the indications for antibiotic prescribing/ dispensing. Thus, the sample size will be driven by the availability of data for patients with exposures and conditions of interest.

## 8.8. Analysis

The analysis will include the calculation of incidence of use of antibiotics (from the WHO AWaRe Access category) and exploring duration of antibiotic use as well as indication for antibiotic prescribing/dispensing as described in section 8.8.3.

### 8.8.1. Federated network analyses

All analyses will be conducted separately for each database, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources and quality control checks will be performed. After all the tests are passed (see section 10 Quality Control), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

The data partners will locally execute the analytics against the OMOP-CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in secure online repository of DTZ (Data Transfer Zone). All results will be locked and timestamped for reproducibility and transparency. The study results of all data sources are checked after which they are made available to the team and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

### 8.8.2. Patient privacy protection

All analyses will be conducted separately for each database, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts <5 will be suppressed when reporting results to comply with the database's privacy protection regulations.

### 8.8.3. Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R packages "*DrugUtilization*" and "*IncidencePrevalence*" developed by DARWIN EU®(37, 38) for the patient-level drug utilisation analyses including patient-level characterisation and for the population-level estimation of drug utilisation, respectively, based on OMOP-CDM mapped data.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤7 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 3**, first row. Note: dose is not considered for this study.

| *Gap era joint mode* | Schematics | Dose in between | Cumulative dose | Cumulative time |
|---|---|---|---|---|
| "first" |  | $d_1$ | $d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$ | $x_1 + x_{12} + x_2$ |
| "second" |  | $d_2$ | $d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$ | $x_1 + x_{12} + x_2$ |
| "zero" |  | 0 | $d_1 \cdot x_1 + d_2 \cdot x_2$ | $x_1 + x_{12} + x_2$ |
| "join" |  | NA | $d_1 \cdot x_1 + d_2 \cdot x_2$ | $x_1 + x_2$ |



**Figure 3**. Gap era joint model.

If two eras start at the same date, the overlapping period will be considered exposed by both.

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription (except for children <1 year). New users will be required to not have been exposed to the drug of interest for at least 30 days prior the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 30 days of no use, the whole exposure is eliminated.

### Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year and month of the index prescription.

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: 0-<1, 1-<2, 2-<12, 12-<18, 18-<46, 46-<70, >=70.

Sex

Results will be presented stratified by sex (male/female).

Indication

Indication will be determined based on recordings of pre-defined conditions (see 8.6.3 – other variables), at the date of the first prescription of the respective drug (index date) [primary definition] or during assessment windows [sensitivity analyses]. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other conditions, the person will be considered having another indication. Characterisation by indication of use will also be stratified by calendar year and by antibiotics class.

## Methods planned to obtain point estimates with confidence intervals of measures of occurrence

**Objective 1 (Incidence rates of antibiotics use)**

Incidence rates calculations will be conducted separately for each antibiotic of interest and antibiotics class.

Incidence calculations

Yearly and monthly incidence rates of the antibiotics of interest will be calculated as the of number of new users after 30 days of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year/month. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription during the study period. Or if they do not have a drug exposure, they will contribute time at risk up as described above in section 8.4 - follow-up. Incidence rates will be given together with 95% Poisson confidence intervals.

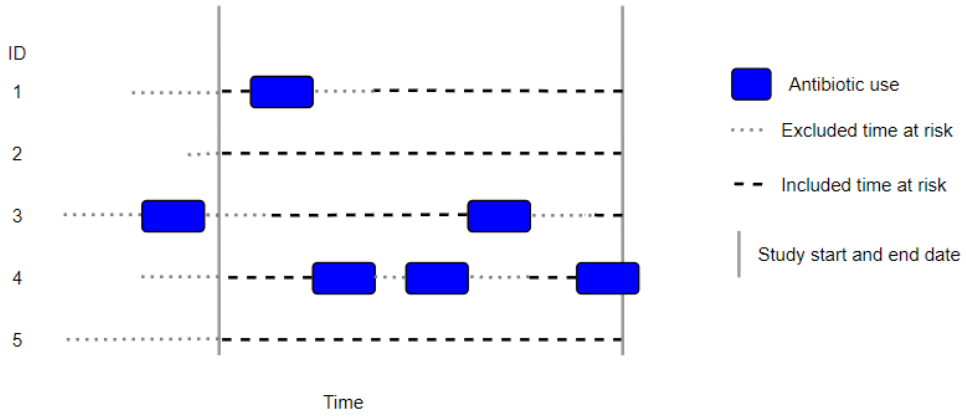


**Figure 4.** Incidence examples for antibiotic use

An illustration of the calculation of incidence of antibiotic use is shown above in **Figure 4**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of antibiotics. Patient ID 2 and 5 are not seen to use antibiotics and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time at risk starting at the day when the washout period of a previous exposure, before study start, has ended, and ending when the next exposure of antibiotic is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of antibiotics count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.

**Objectives 2 and 3 (Duration and indication of antibiotics use)**

New drug user characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows will be provided.

Indication

The number of persons (N, %) with a record of the respective indication of use for the antibiotic of interest will be provided. If a person has a record of more than one specific indication, that person will be included in both specific indication groups. The proportion of indication of antibiotics use over time (2012-2024) stratified by calendar years will be estimated and presented using stacked bar charts.

Treatment duration

Treatment duration will be calculated as the cumulative duration of all exposure era of the antibiotic of interest during the study period from each prescription. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For FinOMOP-THL, duration cannot be calculated due to missing information on quantity or dosing, so treatment duration will not be provided.

Sensitivity analysis

**Table 9**. Sensitivity analyses – rationale, strengths, and limitationsThe sensitivity analysis regarding the exploration of the indication of use is described in **Table 9**.

**Table 9**. Sensitivity analyses – rationale, strengths, and limitations

| Sensitivity analysis | What is being varied? How? | Why? (What do you expect to learn?) | Strengths of the sensitivity analysis compared to the primary | Limitations of the sensitivity analysis compared to the primary |
|---|---|---|---|---|
| Assessment of the indication for use within the window around the index date | Indication of use will be explored in a period of +/-7, -30 - +7 days, and -60 - +7 days of the index date. This will be done only in the unstratified (by calendar year) data. | As indication of use might not always be recorded on the date of prescription of the antibiotic of interest. | Proportion of patients with an indication of use might increase. | Potential misclassification of indication of use if the disease code registered in the week before or after the index date has nothing to do with prescription of the antibiotic of interest. |

### 8.8.4. Output

Output will include a PDF report including an executive summary, and the following tables and figures:

**MAIN RESULTS**

Objective 1 (incidence rates of antibiotics use)

- *Characteristics of the Participants*

**Table shell.** Distribution of study participants' characteristics (number and %, median and IQR, mean and SD) for 10 most prescribed antibiotics across data sources from *WHO AWaRe 'Access'* category.

| Antibiotic name | Characteristic | DK-DHR | FinOMOP THL | IPCI | IQVIA DA Germany | NAJS | SIDIAP |
|---|---|---|---|---|---|---|---|
| **Antibiotic 1** | Overall, N | | | | | | |
| | Median age (IQR) at index date | | | | | | |
| | Mean age (SD) at index date | | | | | | |
| | Age groups, in year N (%) | | | | | | |
| | 0-<1 | | | | | | |
| | 1-<2 | | | | | | |
| | 2-<12 | | | | | | |
| | 12-<18 | | | | | | |
| | 18-<46 | | | | | | |
| | 46-<70 | | | | | | |
| | 70+ | | | | | | |
| | Median index year (IQR) | | | | | | |
| | Sex, N (%) | | | | | | |
| | Male | | | | | | |
| | Female | | | | | | |

- *Incidence rates of the antibiotics prescription from the WHO AWaRe 'Access' category*

**Table shell.** Overall incidence rate per 100,000 PYs (95% confidence intervals) of antibiotics from the WHO AWaRe 'Access' category – 10 most prescribed antibiotics across data sources DK-DHR, FinOMOP THL, IPCI, IQVIA DA Germany, NAJS, and SIDIAP over years 2012-2024.

| DK-DHR | | FinOMOP THL | | IPCI | | IQVIA DA Germany | | NAJS | | SIDIAP | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Antibiotics name | Incidence rates (95% CI) | Antibiotics name | Incidence rates (95% CI) | Antibiotics name | Incidence rates (95% CI) | Antibiotics name | Incidence rates (95% CI) | Antibiotics name | Incidence rates (95% CI) | Antibiotics name | Incidence rates (95% CI) |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Overall incidence rates per 100,000 PYs (95% CI) of all antibiotics from the WHO AWaRe Access category across all data sources will be available in the interactive ShinyApp.

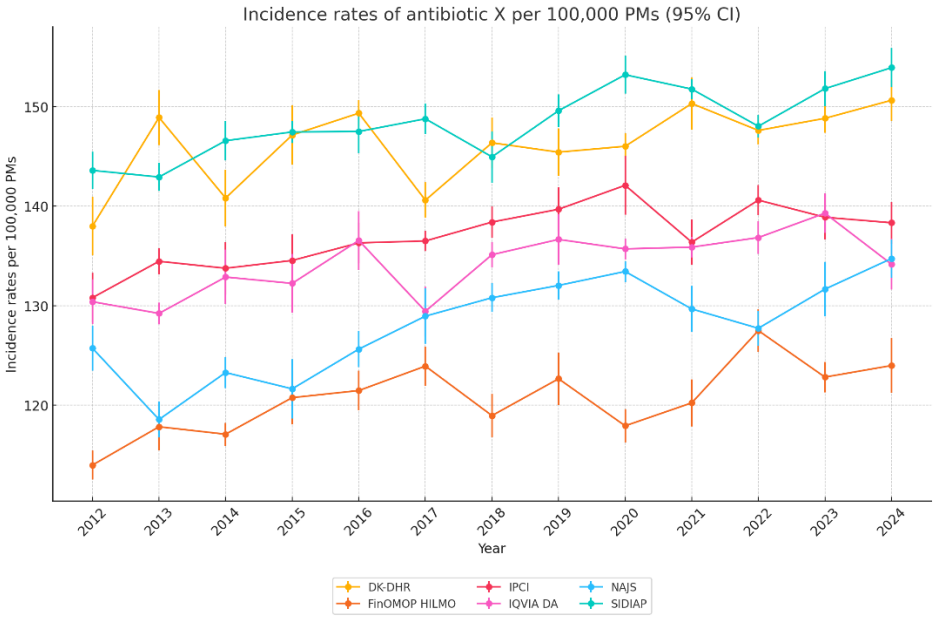


**Figure templates** (one for each 10 most prescribed antibiotics across data sources). Overall yearly incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources DK-DHR, FinOMOP THL, IPCI, IQVIA DA Germany, NAJS, and SIDIAP over years 2012-2024. (The use of coloured lines in the visualizations will reflect the underlying data settings)

Figures showing monthly incidence rates will be included in the Appendix section, as outlined in the Figure Templates of this section below.

- *Incidence rates of the antibiotics from the WHO AWaRe 'Access' category stratified by age group and sex*

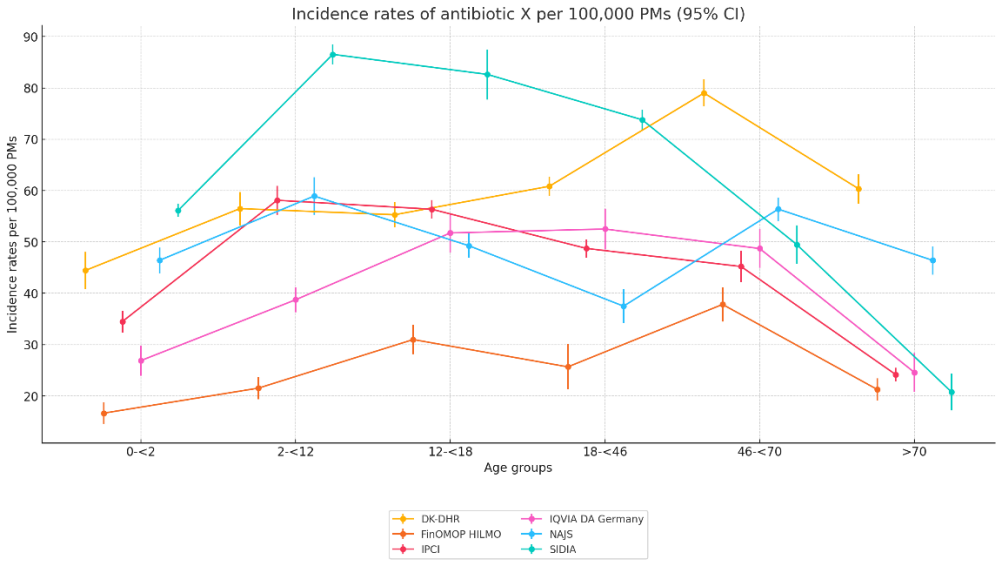


**Figure templates** (one for each 10 most prescribed antibiotics across data sources). Incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources DK-DHR, FinOMOP THL, IPCI, IQVIA DA Germany, NAJS, and SIDIAP stratified by age group (The use of coloured lines in the visualizations will reflect the underlying data settings).

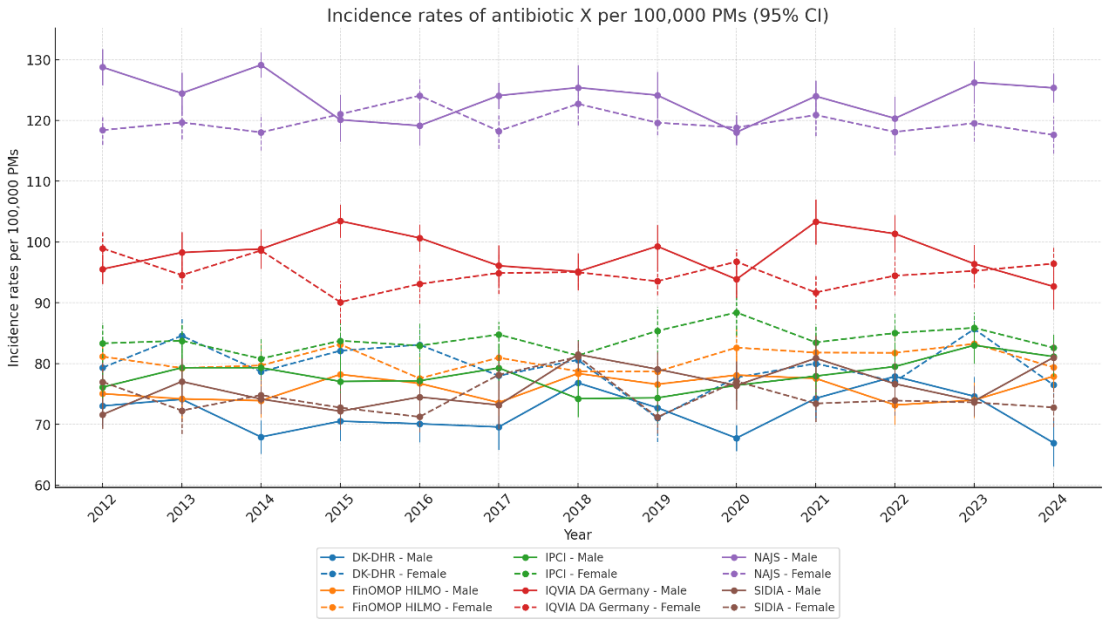


**Figure templates** (one for each 10 most prescribed antibiotics across data sources). Incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources DK-DHR, FinOMOP THL, IPCI, IQVIA DA Germany, NAJS, and SIDIAP stratified by sex (The use of coloured lines in the visualizations will reflect the underlying data settings).

## Objectives 2 and 3 (Duration and indication of antibiotics use)

- *Duration of use*

**Table shell.** Median [P25-P75] duration (in days) of use of antibiotics from the WHO AWaRe 'Access' category –10 most prescribed across data sources.

| | DK-DHR | FinOMOP THL | IPCI | IQVIA DA Germany | NAJS | SIDIAP |
|---|---|---|---|---|---|---|
| Antibiotics name | Duration (median, p25-p75) | Duration (median, p25-p75) | Duration (median, p25-p75) | Duration (median, p25-p75) | Duration (median, p25-p75) | Duration (median, p25-p75) |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

A table displaying the minimum, maximum, median (p25-p75), and mean (SD) duration of use for the 10 most prescribed antibiotics across data sources from the WHO AWaRe Access category by each data source will be presented in Table Shell Appendix below, while data for all antibiotics and on stratification by years will be accessible in the interactive ShinyApp.

- *Indication of use*

**Table shell.** Indications of use (in terms of infections) at index date of 10 most prescribed antibiotics across data sources from WHO AWaRe 'Access' category.

| | DK-DHR | FinOMOP THL | IPCI | IQVIA DA Germany | NAJS | SIDIAP |
|---|---|---|---|---|---|---|
| | **Antibiotic name** | | | | | |
| N overall | | | | | | |
| condition 1 [n (%)] | | | | | | |
| condition 2 [n (%)] | | | | | | |
| condition 3 [n (%)] | | | | | | |
| etc. | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | **Antibiotic name** | | | | | |
| | | | | | | |

Proportion of indications of use over time, presented as stacked percentage charts for individual antibiotics, will be available exclusively through the interactive ShinyApp. A sample template is provided below.

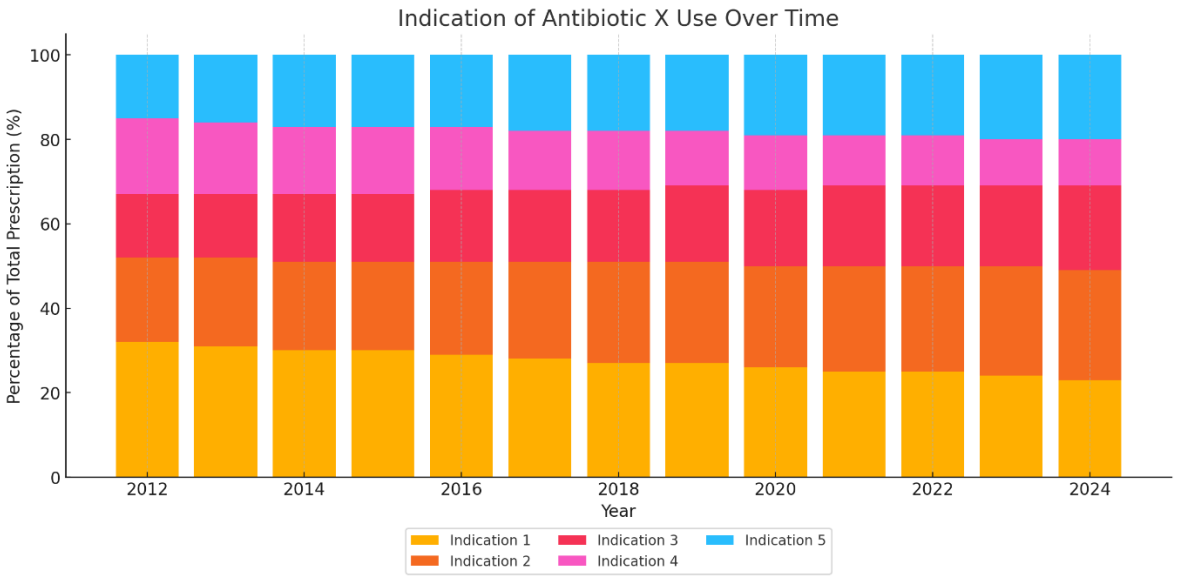


**Figure templates** (one for each 10 most prescribed antibiotics across data sources). Trends in the indications for prescribing Antibiotic X in (data source name) during the study period 2012–2024.

## APPENDIX RESULTS

**Table shell S.** Study attrition of individuals included in each cohort during the study period within each data source.

| | | DK-DHR | | FinOMOP THL | | IPCI | | IQVIA DA Germany | | NAJS | | SIDIAP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Steps | Reasons | Current_n | Excluded | Current_n | Excluded | Current_n | Excluded | Current_n | Excluded | Current_n | Excluded | Current_n | Excluded |
| General | Starting population | | | | | | | | | | | | |
| General | Missing year of birth | | | | | | | | | | | | |
| General | Missing sex | | | | | | | | | | | | |
| General | No observation time available during study period | | | | | | | | | | | | |
| General | Doesn't satisfy age criteria during the study period | | | | | | | | | | | | |
| General | Prior history requirement not fulfilled during study period | | | | | | | | | | | | |
| General | No observation time available after applying age and prior history criteria | | | | | | | | | | | | |
| Incidence | Starting analysis population | | | | | | | | | | | | |
| Incidence | Excluded due to prior event (do not pass outcome washout during study period) | | | | | | | | | | | | |
| Incidence | Not observed during the complete database interval | | | | | | | | | | | | |

**Table shell S.** (one for each data sources). Overall incidence rates per 100,000 PYs (95% confidence intervals) of antibiotics from the WHO AWaRe 'Access' category in the (data source name) data source.

| Data source name | | | | |
|---|---|---|---|---|
| **Antibiotic name** | **Number of participants** | **Follow-up (person-years)** | **Number of prescriptions** | **Incidence Rates/100,000 PYs (95% CI)** |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

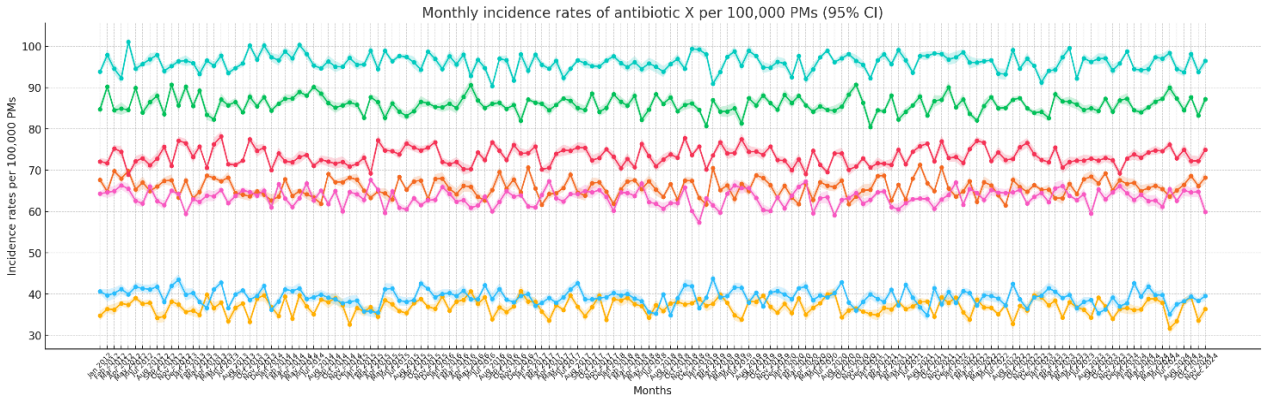


**Figure templates S** (one for each 10 most prescribed antibiotics across data sources). Monthly incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources DK-DHR, FinOMOP THL, IPCI, IQVIA DA Germany, NAJS, and SIDIAP over years 2012-2024 (The use of coloured lines in the visualizations will reflect the underlying data settings).

Details on monthly prescription rates of all antibiotics- including the number of participants, follow-up person-years, and number of prescriptions- will be accessible via an interactive ShinyApp.

**Table shell S.** Duration of use of 10 most prescribed antibiotics across data sources from WHO AWaRe 'Access' category.

| | DK-DHR | FinOMOP THL | IPCI | IQVIA DA Germany | NAJS | SIDIAP |
|---|---|---|---|---|---|---|
| | **Antibiotic name** | | | | | |
| Number of prescriptions | | | | | | |
| Subjects | | | | | | |
| Duration (min-max) | | | | | | |
| Duration (median, p25-p75) | | | | | | |
| Duration (mean, SD) | | | | | | |
| | **Antibiotic name** | | | | | |
| number of prescriptions | | | | | | |
| Subjects | | | | | | |
| Duration (min-max) | | | | | | |
| Duration (median, p25-p75) | | | | | | |
| Duration (mean, SD) | | | | | | |

**Table shell S.** Indications of use (in terms of infections) of 10 most prescribed antibiotics across data sources from WHO AWaRe 'Access' category per data source (in windows around index date: [-7, 7] and [-30, 7]).

| | DK-DHR | | FinOMOP THL | | IPCI | | IQVIA DA Germany | | NAJS | | SIDIAP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Antibiotic name** | | | | | | | | | | | |
| N overall | N | | N | | N | | N | | N | | N | |
| | [-7, 7] | [-30, 7] | [-7, 7] | [-30, 7] | [-7, 7] | [-30, 7] | [-7, 7] | [-30, 7] | [-7, 7] | [-30, 7] | [-7, 7] | [-30, 7] |
| condition 1 [n (%)] | | | | | | | | | | | | |
| condition 2 [n (%)] | | | | | | | | | | | | |
| condition 3 [n (%)] | | | | | | | | | | | | |
| condition 4 [n (%)] | | | | | | | | | | | | |
| etc. | | | | | | | | | | | | |
| | **Antibiotic name** | | | | | | | | | | | |
| N overall | N | | N | | N | | N | | N | | N | |
| condition 1 [n (%)] | | | | | | | | | | | | |
| etc. | | | | | | | | | | | | |

Results from the [-60, +7] window will be available in the interactive Shiny app, depending on the quality of the results. If the number of missing indications is low, we will also include them in the report.

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the pdf report mentioned above.

## 8.9. Evidence synthesis

Results from the analyses described in section 8.8 will be presented separately for each data source. No meta-analysis of results will be conducted.

# 9. DATA MANAGEMENT

## 9.1. Data management

All databases have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study will be written in R and will use standardized analytics wherever possible. Each data partner will execute the study code against their database containing patient-level data and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

## 9.2. Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

# 10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). All data partners have run the OHDSI Data Quality Dashboard as part of the onboarding process (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of

data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level. A pharmacist will review the codes of the antibiotics of interest.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.

The study code will be based on two R packages currently being developed to (1) estimate Incidence and (2) characterise drug utilisation using the OMOP common data model. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

# 11. LIMITATIONS OF THE RESEARCH METHODS

This study will be informed by routinely collected health care data and so data quality issues have to be considered.

In particular, a recording of a prescription does not mean that the patient took the drug. In addition, assumptions around the duration of drug use will be unavoidable. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided. (For this reason, data from FinOMOP THL will not be used for objective 2)

The specific reason for prescribing the antibiotics may not be directly recorded in the databases. Instead, the indication will likely be inferred using a proxy based on predefined conditions documented around the therapy initiation date, which may result in incomplete recording of potential indications. Additionally, variations in how events used for patient characterization are documented across databases may persist. While infection categories will be defined using the SNOMED dictionary, not all infections may fit within these predefined categories.

While OMOP provides mappings to established vocabularies like SNOMED, inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data analysis in different databases.

Additionally, the results estimated from this study will only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical purpose rather than primarily for research use. Consequently, using six primary and secondary care data sources from Denmark, Finland, the Netherlands, Germany, Croatia, and Spain limits generalisability to those countries.

# 12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management, and reporting of individual cases of adverse events/adverse reactions.

# 13. GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective local Institutional Review Boards (IRB) to perform this study, with the exception of DK-DHR Denmark and Croatian NAJS which will not require any further specific approvals to undertake this study.

# 14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

# 15. REFERENCES

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# 16. APPENDIXES

**Appendix I**: Concepts set for study variables

Exposures concept name and concept IDs definition is listed in the **Table S1**.

**Table S1.** List of concept IDs for antibiotics from WHO AWaRe 'Access' category exposure definition.

| | Antibiotics of Access category | Class | ATC code | Concept id (including descendants) | Concept Name | vocabulary |
|---|---|---|---|---|---|---|
| 1 | Amikacin | Aminoglycosides | J01GB06 | 21602999 | Amikacin | RxNorm |
| 2 | Amoxicillin | Penicillins | J01CA04 | 21602823 | Amoxicillin | RxNorm |
| 3 | Amoxicillin/clavulanic acid | Beta-lactam/beta-lactamase-inhibitor | J01CR02 | 21602863 | Amoxicillin and beta-lactamase inhibitor | RxNorm |
| 4 | Ampicillin | Penicillins | J01CA01 | 21602820 | Ampicillin | RxNorm |
| 5 | Ampicillin/sulbactam | Beta-lactam/beta-lactamase-inhibitor | J01CR01 | 21602862 | Ampicillin and beta-lactamase inhibitor | RxNorm |
| 6 | Azidocillin | Penicillins | J01CE04 | 21602844 | Azidocillin | RxNorm |
| 7 | Bacampicillin | Penicillins | J01CA06 | 21602825 | Bacampicillin | RxNorm |
| 8 | Benzathine-benzylpenicillin | Penicillins | J01CE08 | 21602848 | Benzathine benzylpenicillin | RxNorm |
| 9 | Benzylpenicillin | Penicillins | J01CE01 | 21602841 | Benzylpenicillin | RxNorm |
| 10 | Brodimoprim | Trimethoprim-derivatives | J01EA02 | 21602932 | Brodimoprim | RxNorm |
| 11 | Cefacetrile | First-generation-cephalosporins | J01DB10 | 21602879 | Cefacetrile | RxNorm |
| 12 | Cefadroxil | First-generation-cephalosporins | J01DB05 | 21602874 | Cefadroxil | RxNorm |
| 13 | Cefalexin | First-generation-cephalosporins | J01DB01 | 21602870 | Cephalexin | RxNorm |
| 14 | Cefaloridine | First-generation-cephalosporins | J01DB02 | 21602871 | Cephaloridine | RxNorm |
| 15 | Cefalotin | First-generation-cephalosporins | J01DB03 | 21602872 | Cephalothin | RxNorm |

| | | | | | | |
|---|---|---|---|---|---|---|
| 16 | Cefapirin | First-generation-cephalosporins | J01DB08 | 21602877 | Cephapirin | RxNorm |
| 17 | Cefatrizine | First-generation-cephalosporins | J01DB07 | 21602876 | Cefatrizine | RxNorm |
| 18 | Cefazedone | First-generation-cephalosporins | J01DB06 | 21602875 | Cefazedone | RxNorm |
| 19 | Cefazolin | First-generation-cephalosporins | J01DB04 | 21602873 | Cefazolin | RxNorm |
| 20 | Cefradine | First-generation-cephalosporins | J01DB09 | 21602878 | Cephradine | RxNorm |
| 21 | Cefroxadine | First-generation-cephalosporins | J01DB11 | 21602880 | Cefroxadine | RxNorm |
| 22 | Ceftezole | First-generation-cephalosporins | J01DB12 | 21602881 | Ceftezole | RxNorm |
| 23 | Chloramphenicol | Amphenicols | J01BA01 | 21602815 | Chloramphenicol | RxNorm |
| 24 | Clindamycin | Lincosamides | J01FF01 | 21602985 | Clindamycin | RxNorm |
| 25 | Clometocillin | Penicillins | J01CE07 | 21602847 | Clometocillin | RxNorm |
| 26 | Cloxacillin | Penicillins | J01CF02 | 21602854 | Cloxacillin | RxNorm |
| 27 | Dicloxacillin | Penicillins | J01CF01 | 21602853 | Dicloxacillin | RxNorm |
| 28 | Doxycycline | Tetracyclines | J01AA02 | 21602800 | Doxycycline | RxNorm |
| 29 | Epicillin | Penicillins | J01CA07 | 21602826 | Epicillin | RxNorm |
| 30 | Flucloxacillin | Penicillins | J01CF05 | 21602857 | Floxacillin | RxNorm |
| 31 | Furazidin | Nitrofuran derivatives | J01XE03 | 45893495 | Furazidine | RxNorm |
| 32 | Gentamicin | Aminoglycosides | J01GB03 | 21602996 | Gentamicin | RxNorm |
| 33 | Hetacillin | Penicillins | J01CA18 | 21602837 | Hetacillin | RxNorm |

| | | | | | | |
|---|---|---|---|---|---|---|
| 34 | Mecillinam | Penicillins | J01CA11 | 21602830 | Amdinocillin | RxNorm |
| 35 | Metampicillin | Penicillins | J01CA14 | 21602833 | Methampicillin | RxNorm |
| 36 | Meticillin | Penicillins | J01CF03 | 21602855 | Meticillin | RxNorm |
| 37 | Metronidazole_IV | Imidazoles | J01XD01 | 21603054 | Metronidazole | RxNorm |
| 38 | Metronidazole_oral | Imidazoles | P01AB01 | 21604857 | Metronidazole | RxNorm |
| 39 | Nafcillin | Penicillins | J01CF06 | 43534792 | Nafcillin | RxNorm |
| 40 | Nifurtoinol | Nitrofuran derivatives | J01XE02 | 21603059 | Nifurtoinol | RxNorm |
| 41 | Nitrofurantoin | Nitrofuran-derivatives | J01XE01 | 21603058 | Nitrofurantoin | RxNorm |
| 42 | Ornidazole_IV | Imidazoles | J01XD03 | 21603056 | Ornidazole | RxNorm |
| 43 | Ornidazole_oral | Imidazoles | P01AB03 | 21604859 | Ornidazole | RxNorm |
| 44 | Oxacillin | Penicillins | J01CF04 | 21602856 | Oxacillin | RxNorm |
| 45 | Penamecillin | Penicillins | J01CE06 | 21602846 | Penamecillin | RxNorm |
| 46 | Phenoxymethylpenicillin | Penicillins | J01CE02 | 21602842 | Penicillin V | RxNorm |
| 47 | Pivampicillin | Penicillins | J01CA02 | 21602821 | Pivampicillin | RxNorm |
| 48 | Pivmecillinam | Penicillins | J01CA08 | 21602827 | Amdinocillin pivoxil | RxNorm |
| 49 | Procaine-benzylpenicillin | Penicillins | J01CE09 | 21602849 | Penicillin G | RxNorm |
| 50 | Propicillin | Penicillins | J01CE03 | 21602843 | Propicillin | RxNorm |
| 51 | Secnidazole | Imidazoles | P01AB07 | 21604863 | Secnidazole | RxNorm |

| | | | | | | |
|---|---|---|---|---|---|---|
| 52 | Spectinomycin | Aminocyclitols | J01XX04 | 21603064 | Spectinomycin | RxNorm |
| 53 | Sulbactam | Beta-lactamase-inhibitors | J01CG01 | 21602859 | Sulbactam | RxNorm |
| 54 | Sulfadiazine | Sulfonamides | J01EC02 | 21602946 | Sulfadiazine | RxNorm |
| 55 | Sulfadiazine/tetroxoprim | Sulfonamide-trimethoprim-combinations | J01EE06 | 21602966 | Sulfadiazine and tetroxoprim | RxNorm |
| 56 | Sulfadiazine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE02 | 21602962 | Sulfadiazine and trimethoprim | RxNorm |
| 57 | Sulfadimethoxine | Sulfonamides | J01ED01 | 21602950 | Sulfadimethoxine | RxNorm |
| 58 | Sulfadimidine | Sulfonamides | J01EB03 | 21602937 | Sulfamethazine | RxNorm |
| 59 | Sulfadimidine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE05 | 21602965 | Sulfadimidine and trimethoprim | RxNorm |
| 60 | Sulfafurazole | Sulfonamides | J01EB05 | 21602939 | Sulfafurazole | RxNorm |
| 61 | Sulfaisodimidine | Sulfonamides | J01EB01 | 21602935 | Sulfaisodimidine | RxNorm |
| 62 | Sulfalene | Sulfonamides | J01ED02 | 21602951 | Sulfalene | RxNorm |
| 63 | Sulfamazone | Sulfonamides | J01ED09 | 21602958 | Sulfamazone | RxNorm |
| 64 | Sulfamerazine | Sulfonamides | J01ED07 | 21602956 | Sulfamerazine | RxNorm |
| 65 | Sulfamerazine/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE07 | 21602967 | Sulfamerazine and trimethoprim | RxNorm |
| 66 | Sulfamethizole | Sulfonamides | J01EB02 | 21602936 | Sulfamethizole | RxNorm |
| 67 | Sulfamethoxazole | Sulfonamides | J01EC01 | 21602945 | Sulfamethoxazole | RxNorm |
| 68 | Sulfamethoxazole/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE01 | 21602961 | Sulfamethoxazole and trimethoprim | RxNorm |

| | | | | | | |
|---|---|---|---|---|---|---|
| 69 | Sulfamethoxypyridazine | Sulfonamides | J01ED05 | 21602954 | Sulfamethoxypyridazine | RxNorm |
| 70 | Sulfametomidine | Sulfonamides | J01ED03 | 21602952 | Sulfametomidine | RxNorm |
| 71 | Sulfametoxydiazine | Sulfonamides | J01ED04 | 21602953 | Sulfametoxydiazine | RxNorm |
| 72 | Sulfametrole/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE03 | 21602963 | Sulfametrole and trimethoprim | RxNorm |
| 73 | Sulfamoxole | Sulfonamides | J01EC03 | 21602947 | Sulfamoxole | RxNorm |
| 74 | Sulfamoxole/trimethoprim | Sulfonamide-trimethoprim-combinations | J01EE04 | 21602964 | Sulfamoxole/trimethoprim | RxNorm |
| 75 | Sulfanilamide | Sulfonamides | J01EB06 | 21602940 | Sulfanilamide | RxNorm |
| 76 | Sulfaperin | Sulfonamides | J01ED06 | 21602955 | Sulfaperin | RxNorm |
| 77 | Sulfaphenazole | Sulfonamides | J01ED08 | 21602957 | Sulfaphenazole | RxNorm |
| 78 | Sulfapyridine | Sulfonamides | J01EB04 | 21602938 | Sulfapyridine | RxNorm |
| 79 | Sulfathiazole | Sulfonamides | J01EB07 | 21602941 | Sulfathiazole | RxNorm |
| 80 | Sulfathiourea | Sulfonamides | J01EB08 | 21602942 | Sulfathiourea | RxNorm |
| 81 | Sultamicillin | Beta-lactam/beta-lactamase-inhibitor | J01CR04 | 21602865 | Sultamicillin | RxNorm |
| 82 | Talampicillin | Penicillins | J01CA15 | 21602834 | Talampicillin | RxNorm |
| 83 | Tetracycline | Tetracyclines | J01AA07 | 21602805 | Tetracycline | RxNorm |
| 84 | Thiamphenicol | Amphenicols | J01BA02 | 21602816 | Thiamphenicol | RxNorm |
| 85 | Tinidazole_IV | Imidazoles | J01XD02 | 21603055 | Tinidazole | RxNorm |
| 86 | Tinidazole_oral | Imidazoles | P01AB02 | 21604858 | Tinidazole | RxNorm |

| | | | | | | |
|---|---|---|---|---|---|---|
| 87 | Trimethoprim | Trimethoprim-derivatives | J01EA01 | 21602931 | Trimethoprim | RxNorm |

*Non-systemic antibiotics will be excluded, except for bacterial eye infections.

Conditions concept name and concept IDs definition is listed in the **Table S2.**

**Table S2.** Preliminary list of concept IDs for conditions of interest as an indication of antibiotic use.

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| Eye infections | 378425, 438411, 4134613, 379019 | Blepharitis, Endophthalmitis, Eye infection, Conjunctivitis | 42572963, 42598813, 42598791, 4220916, 42593602, 42593599, 42573137 | SNOMED |
| Oral and dental infections | 134074, 141608, 4025325, 4103655, 4123730, 4170116, 4281516, 4122209 | Cellulitis of oral soft tissues, Periodontitis, Periapical abscess, Dental abscess, Chronic sialadenitis, Oral infection, Gingivitis, Oral herpes simplex infection | 42572696, 42598955, 42598582, 42574126, 954229, 42593388, 42598732, 42600110 | SNOMED |
| Pharyngitis | 4226263 | Pharyngitis | 4123082, 37397178, 4009043, 4049660 | SNOMED |
| Otitis media | 372328 | Otitis media | 42598429 | SNOMED |
| Sinusitis | 4283893 | Sinusitis | 42573224 | SNOMED |
| Bronchitis | 4105601, 255841, 4279922, 4233924, 260139 | Purulent bronchitis, Chronic bronchitis, Septic bronchitis, Pneumococcal bronchitis, Acute bronchitis | 765431, 261889, 37206130, 4230358, 4172303 | SNOMED |
| Pneumonia | 4050869, 255848 | Atypical pneumonia, Pneumonia | 42598655, 42573181, 42572881, 42599199, 42599060, 42598979, 42573179, 42573178, 42573020, 42572644, 42599561, 42598991, 42598908, 42593423, 42600053, 42573349, 42573218, 42600167 | SNOMED |
| COPD/exacerbation of chronic obstructive pulmonary disease | 255573, 257004, 4115044 | Chronic obstructive pulmonary disease, Acute exacerbation of chronic obstructive pulmonary disease, Acute infective | - | SNOMED |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | exacerbation of chronic obstructive pulmonary disease | | |
| Asthma/exacerbation of asthma | 43530693, 317009 | Acute exacerbation of chronic obstructive pulmonary disease with asthma, Asthma | - | SNOMED |
| Endocarditis | 441589 | Endocarditis | 42597024, 42597025, 42597026, 42574210 | SNOMED |
| Acute infectious diarrhoea or gastroenteritis | 197484, 198337, 4101468, 4167082, 193688 | Diarrhea of presumed infectious origin, Infectious diarrheal disease, Gastroenteritis, Bacterial gastroenteritis, Clostridioides difficile infectionPurulent bronchitis, Diarrhea of presumed infectious origin, Infectious diarrheal disease, Gastroenteritis, Bacterial gastroenteritis, Clostridioides difficile infection | 42598601, 42594405, 42598710, 42595096, 4146457, 196895, 42572970, 42572684, 42597110, 42573165, 42599178, 42599162, 42599037, 42572975, 42572901, 42599097, 42572974, 42598915, 42572896, 42599123, 42598906, 42573209 | SNOMED |
| Enteric fever | 192819, 195177 | Typhoid fever, Paratyphoid fever | - | SNOMED |
| Intra-abdominal infections | 4141224, 4178110, 4276784, 4340497, 4192640, 4171019, 4088114, 3187323, 3176245, 195856, 196152, 192956, 42574016, 201901 | Diverticulitis, Traumatic perforation of large intestine, Traumatic perforation of small intestine, Infected pancreatic necrosis, Pancreatitis, Abdominal visceral abscess, Postoperative intra-abdominal abscess, Right upper abdominal abscess, Right lower quadrant abdominal abscess, Cholangitis, Peritonitis, Cholecystitis, Clostridial colitis, Abscess of liver | 42573163, 42573162, 42599237, 42595100, 42573164, 4342877, 4341774, 42599158, 42574230, 42597029, 42597105, 42597359, 42599235, 42597055, 42573348, 954117 | SNOMED |
| Urinary tract infections | 195862, 81902, 198199, 195588, 77340, 4142194, 198192 | Urethritis, Urinary tract infectious disease, Pyelonephritis, Cystitis, Genitourinary tract | 42600293, 42598600, 42593547, 42598968, 42573007, 42600389, 42572888, 3194810, 4056622, 4047937, 607157, 4032450, 42600089, | SNOMED |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | infection in pregnancy, Renal abscess, Renal and perinephric abscess | 4100954, 606982, 4239213, 4030507, 37017585, 4128374, 37017217, 954561 | |
| Other genito-urinary infection | 194997, 78193, 199067, 4312329, 4149084, 196163, 4171915, 4150043 | Prostatitis, Orchitis and epididymitis, Female pelvic inflammatory disease, Perimetritis, Vaginitis, Cervicitis and endocervicitis, Orchitis, Epididymitis | 42599058, 42597060, 954079, 42598794, 42573188, 42599971, 42573334, 42599837 | SNOMED |
| Sexually transmitted infections | 79732, 434872, 440647, 4057315, 37309610, 37312673, 42536585, 44788692, 44789331, 4276586, 439727 | Genitourinary chlamydia infection, Infection by Trichomonas, Sexually transmitted infectious disease, HVS culture - trichomonas vaginalis, Gonorrhea of lower genitourinary tract, Inflammation of pelvis caused by Chlamydia trachomatis, Infection of genitourinary system caused by Neisseria gonorrhoeae, Trichomonas seen, Trichomonas vaginalis contact, Finding of HIV status, Human immunodeficiency virus infection | 4056400, 197203, 443054, 4080339, 4056400, 4157531, 4080333, 4084822, 4322865, 4242126, 42599092, 42598638, 3200792, 4013105 | SNOMED |
| Meningitis and encephalitis | 435785, 378143 | Meningitis, Encephalitis | 42593067, 42599865, 42599239, 42596612, 42574231, 42596575, 42596610, 42596611, 42596666, 42596655, 42596657, 42599838, 42572953, 42598680, 42572787, 42573325, 42597997, 42599011, 42599000, 42596629, 42572712, 42598867, 42597146, 42598804 | SNOMED |
| Sepsis or septic shock | 132797, 196236 | Sepsis, Septic shock | - | SNOMED |
| Febrile neutropenia | 4250734 | Febrile neutropenia | - | SNOMED |
| Osteomyelitis | 141663 | Osteomyelitis | 42598482, 42597272, 42597177, 42597205, 42574042, 42597284, 42597165, 42597202, | SNOMED |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | | 42597228, 42597288, 42597289, 42597232, 42574047, 42597209, 42597155 | |
| Septic arthritis | 4180167 | Infectious disorder of joint | 42598859, 42599075, 42598482, 42597189, 42598680, 42573193, 42598483, 42597162, 42597218, 42597169, 42574034, 42599633, 42597196, 42597291, 42597269, 42598723, 42599281, 42597284, 42574047, 42575811 | SNOMED |
| Skin and soft tissue infections | 435740, 442013, 4029483, 4030849, 4046789, 4090679, 4096471, 4096472, 4096474, 4141909, 4151842, 4262920, 4159742, 4153877, 4183970, 4211967, 4237450, 4297984, 36715557, 44806474, 44806641, 440638, 435613, 4200289, 4300385, 4320030 | Tetanus, Burn, Anaplasmosis, Wound abscess, Penetrating wound, Pasteurella septic infection (cat or dog bite, Deep wound, Penetrating wound, Deep avulsion wound, Bite wound, Bite - wound, Skin ulcer, Diabetic foot ulcer, Post-traumatic wound infection, Wound dirty, Deep wound, Postoperative wound infection, Local infection of wound, Pyogenic infection of skin and subcutaneous tissues caused by bacterium, O/E - wound necrotic, Infection associated with wound, Lyme disease, Cellulitis, Preseptal cellulitis, Vulval cellulitis, Soft tissue infection | 4335890, 42596707, 42599845, 42596392, 42599652, 42574046, 46270494, 3657767, 3657768, 4161830, 3657864, 36714565, 4146111, 380944, 36714497, 4028254, 37209315, 608803, 37209444, 608804, 37108901, 4287838, 372550, 442552, 3654936, 375187, 378352, 4244336, 4231740, 4345914, 761333, 761332, 765217, 37209445, 765280, 765071, 37310072, 37309999, 37309947, 37310064, 37310055, 37310010, 37309965, 37310053, 37309987, 37310051, 36683380, 4335889, 372842, 4253626, 4218443, 4225881, 4222588, 4224271, 4222419, 4294573, 4222420, 4222421, 4224272, 4096836, 4294574, 4300324, 4300325, 4293288, 4294575, 4293289, 4220840, 4298991, 4300326, 4294576, 4305732, 4298994, 4133972, 4082049, 4078538, 4167083, 80946, 4222430, 4226003, 4222431, 4222597, 4300328, 4226004, 134865, 4300335, 4294703, 4163280, 133141, 4183870, 4294841, 4094067, 4294578, 4298995, 4293290, 4060657, 4078931, 4300215, 4144953, 4028324, 40490394, 40491348, 40490302, 40489357, 4291603, 4051339, 192361, 4110039, 4137452, 3654661, 4026017, 198076, 197790, 4342876, 4342877, | SNOMED |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | | 4144034, 196345, 443796, 4341774, 4198021, 199863, 198189, 44808741, 44808743, 198345, 194268, 37311895, 37311635, 3176778, 36683379, 37311636, 37310070, 37310004, 37309946, 37310063, 37310054, 37310009, 37309964, 42599710, 42598686, 42572881, 42598451, 42598458, 42596424, 42592702, 42572887, 42599711, 42599271, 42592701, 42574134, 42600167, 42598622, 42598579, 42572604, 42574135, 42598463, 42598796, 42596302, 42599966, 42573149, 954118, 4239213, 4338751, 4344052, 37161097, 42536747, 37017777, 4298735, 4082050, 3655666, 3655670, 607399, 4122211, 4300224, 4301039, 4294449, 4112116, 134074, 4124365, 4080460, 4124508, 3657965, 4122755, 4122209, 4124509, 4122759, 4122756, 4122760, 4095882, 4096496, 4122757, 4122758, 4056925, 4122210, 4122751, 4126928, 761331, 37209443, 761784, 761330, 761334, 761335, 761336, 4103893, 4265858, 42599147, 42573184, 42572969, 42572859, 42573180, 42593793, 42597178, 42597044, 4253627, 376028, 4209134, 4159754, 4103653, 4089879, 4265439, 4163288, 761329, 761328, 4106896, 4259503, 442757, 4312036, 4265742, 4238336, 376422, 765528, 764828, 765739, 4171248, 4084947, 36717459, 373870, 4146848, 4132505, 4171250, 378753, 4306683, 4300208, 4348434, 4302049, 4098881, 4009923, 4088086, 380038, 4093292, 137213, 4141481, 140027, 132835, 4080331, 4160328, 137785, 4212782, 4239344, 4243325, 760174, 4217694, | |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | | 4249876, 4202370, 4201753, 619343, 4084948, 4291601, 760929, 4084816, 4080330, 4347555, 4177636, 4148102, 4345473, 4084817, 4080770, 4291602, 4081909, 4142828, 4185025, 4182586, 760906, 760907, 44810378, 4345474, 4294439, 4300214, 4294440, 3656108, 4111926, 4124510, 4200244, 4080745, 4172458, 45757655, 4234876, 4122212, 4080744, 4270604, 4070648, 4298988, 4084967, 4142837, 4082052, 4270605, 4080315, 609055, 36687211, 609054, 4163426, 4067324, 4183059, 4174374, 4188361, 4010883, 4204375, 4321597, 4182398, 4185834, 4225882, 37310052, 37309986, 37310050, 37310012, 4052375, 4343215, 4155027, 4152958, 4181310, 4151521, 4155028, 4152956, 4151520, 40483694, 137441, 4052230, 4052650, 40408433, 436859, 4171380, 443761, 4171058, 4221875, 4219819, 4032628, 4178891, 4308445, 4210750, 4065912, 80883, 444103, 142016, 4140541, 4213341, 442640, 4093263, 4183151, 132483, 194799, 4198074, 760765, 4246106, 42709771, 443594, 439197, 4195716, 4148533, 4149402, 760764, 4031829, 4187237, 4300986, 442351, 4066406, 137425, 4262214, 444436, 42596301, 42573954, 42597130, 42597138, 42572756, 42598859, 42599243, 42599065, 42572696, 42572847, 42598627, 42599516, 42599028, 42572939, 42599020, 42596299, 42592867, 42596077, 42573163, 42573187, 42572772, 42572968, 42573162, 42599237, 42572450, 42572963, 42574126, 42598916, 42598956, 42598813, 42572960, 42574044, 42572894, 42599106, | |

| Phenotypes | Concept IDs (including descendants) * | Concept names | Exclude concept IDs | Vocabulary |
|---|---|---|---|---|
| | | | 42600083, 42573137, 42599273, 42596405, 42596392, 42599606, 42573164, 42598791, 42598582, 42593338, 42593339, 42599712, 42593342, 42572950, 42599373, 42599866, 42599502, 42598589, 42599043, 42596300, 42572953, 42598732, 42597046, 42597037, 42597036, 705175, 4136355 | |
| Localized acute bacterial lymphadenitis | 316084 | Lymphadenitis | 313989, 4081069, 4210780, 4141212, 435234, 4256233, 40487345, 4212138, 42598890, 42572895, 42599003 | SNOMED |
| Surgical prophylaxis | 4226249, 4186104, 4307296, 3655883 | Administration of prophylactic antibiotic, Antibiotic prophylaxis indicated, Antibiotic prophylaxis recommended, Prescription of antibiotic prophylaxis | 2108648, 2108647, 4147949, 4015136, 4101042, 3655883, 4143697, 44783513, 4077050 | SNOMED |

*Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor.

Before finalizing the concept sets, CohortDiagnostics will run on cohorts created using the initial concept sets to check code counts and patient characteristics which might give indications to adjust the concept sets.

**Appendix II**: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

# ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

**Study title:** DARWIN EU® - Drug utilisation study on antibiotics in the 'Access' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use

**EU PAS Register® number:** EUPAS1000000663
**Study reference number (if applicable):** P3-C1-022

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 8.3 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 8.3 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim report(s) | ☐ | ☐ | ☒ | |
| 1.1.5 Registration in the EU PAS Register® | ☐ | ☒ | ☐ | |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 5 |

Comments:

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| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | |
| 2.1.1 Why is the study conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 6 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 7 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 8.5 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 8.1 |
| 3.2 | Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 8.2 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 8.8 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☐ | ☐ | ☒ | |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 12 |

Comments:

| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 8.2 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 8.3 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 8.5 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 8.2 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 8.6 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 8.4 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 8.5 |

Comments:

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.1 | Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 8.6 |
| 5.2 | Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 | Is exposure categorised according to time windows? | ☐ | ☐ | ☒ | |
| 5.4 | Is intensity of exposure addressed? (e.g. dose, duration) | ☐ | ☐ | ☒ | |
| 5.5 | Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 6: Outcome definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 6.1 | Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☐ | ☐ | ☒ | |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☐ | ☐ | ☒ | |
| 6.3 | Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 6.4 | Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 7: Bias** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 7.1 | Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☐ | ☐ | ☒ | |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☐ | ☐ | ☒ | |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 8: Effect measure modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 8.6 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☐ | ☐ | ☒ | |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.2 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 8.6 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event) | ☐ | ☐ | ☒ | |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 8.2 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 8.6 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | |
| 9.3.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.2 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 8.2 |

Comments:

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 8.8 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 8.7 |
| 10.3 Are descriptive analyses included? | ☐ | ☐ | ☒ | |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 8.8 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☐ | ☒ | |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☐ | ☒ | |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☐ | ☐ | ☒ | |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 10 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of:<br>12.1.1 Selection bias?<br>12.1.2 Information bias?<br>12.1.3 Residual/unmeasured confounding?<br>(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☒<br>☒<br>☐ | ☐<br>☐<br>☐ | ☐<br>☐<br>☒ | 11 |
| 12.2 Does the protocol discuss study feasibility?<br>(e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☒ | ☐ | ☐ | 8.7 |

Comments:

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| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have the requirements of the Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 13 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 9.2 |

Comments:

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| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 4 |

Comments:

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| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 14 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☐ | ☐ | ☒ | |

Comments:

Name of the main author of the protocol: Marzyeh Amini

Date: 18/04/2025

Signature: M. Amini