Study Protocol

P3-C1-023

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

19/09/2025

Version 3.0

Public

CONTENTS

Study title	DARWIN EU® - Drug utilisation study on antibiotics in the 'Reserve' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use
Protocol version	V3.0
Date	19/09/2025
EUPAS number	EUPAS1000000664
Active substance	All antibiotics listed under the WHO AWaRe 'Reserve' 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 'Reserve' 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 specific objectives are: 1. To investigate the incidence of prescription of individual antibiotics and antibiotics class (from the WHO AWaRe 'Reserve' category), stratified by age, sex, calendar year/month during the study period 2012-2024. 2. To characterise individual antibiotics and antibiotics class (WHO AWaRe 'Reserve' category 2023) use by duration of use over the study period 2012-2024. 3. To characterise individual antibiotic and antibiotics class (WHO AWaRe 'Reserve' category 2023) use by indication of use stratified by calendar year over the period 2012-2024.
Countries of study	Denmark, Greece, France, Hungary, Italy, Portugal, Spain
Authors	M. Amini, m.amini@darwin-eu.org K. Verhamme, k.verhamme@darwin-eu.org Nicholas Hunt, n.hunt@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
AMR	Antimicrobial Resistance
AWaRe	Access, Watch, and Reserve
ASPs	Antimicrobial Stewardship Programs
CC	Coordinating centre
CDM	Common Data Model
CDWBordeaux	Clinical Data Warehouse of Bordeaux University Hospital
COPD	Chronic obstructive pulmonary disease
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DUS	Drug Utilization Study
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
EMDB–ULSEDV	Egas Moniz Health Alliance database - Entre o Douro e Vouga
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
LRTI	Lower respiratory tract infection
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PGH	Papageorgiou General Hospital
POLIMI	Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

RxNorm	Medical prescription normalized
SD	Standard Deviation
SNOMED	Systematized Nomenclature of Medicine
SUCD	Semmelweis University Clinical Data
WHO	World Health Organisation
WONCA	World Organization of Family Doctor

1. TITLE

DARWIN EU® - Drug utilisation study on antibiotics in the 'Reserve' 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 Katia Verhamme Nicholas Hunt	Erasmus MC
Data Scientists	Ger Inberg Ioanna Nika	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner Name*	**Name of Members**	**Organisation**
CDWBordeaux	Romain Griffer Guillaume Verdy	CHU Bordeaux
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency
EMDB-ULSEDV	Tiago Taveira Ana Pinto Joao Firmino Machado	Clinical Academic Center Egas Moniz (CAC-EMHA)
IMASIS	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	PSMAR
PGH	Pantelis Natsiavas Anastasia Farmaki Alexandros Rekkas Achilleas Chytas	Papageorgiou General Hospital
POLIMI	Gianluigi Galli	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - POLIMI
SUCD	Ágota Mészáros Bagyura Zsolt István Tibor Héja	Semmelweis University

*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 'Reserve' 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 Reserve category comprises critically important antibiotics that serve as last-resort options for treating confirmed or suspected infections caused by multidrug-resistant organisms. These antibiotics are recommended only when all alternative treatments have failed, due to their importance in combating life-threatening infections such as those caused by carbapenem-resistant Enterobacteriaceae and other extended-spectrum beta-lactamase producing bacteria. As of the 2023 update, the Reserve category includes 27 antibiotics, reflecting the WHO's strategic effort to curb antimicrobial resistance (AMR) by promoting their strict and judicious use in both inpatient and outpatient settings. The inclusion of antibiotics in this group aims to preserve their efficacy by reducing overuse and misuse, particularly in low-resource settings where AMR surveillance may be limited.(1, 2)

The DARWIN EU® P1-C1-003 study focused on the Watch category but there is now interest in including also the other category (Reserve) 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 WHO AWaRe 'Reserve' category 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 'Reserve' 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?

Objectives

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

- New drug user cohort study (Objectives 2 and 3, 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 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.

Because hospital records often only cover from first to last visit, patients from hospital data sources (CDW Bordeaux, IMASIS, SUCD, POLIMI, EMDB - ULSEDV, PGH) with less than 365 days of prior observation will still be included in the analysis.

Study period

Study period will start from January 2012 to the end of December 2024, or up to the latest date of data availability. In the POLIMI data source, accurate data will be available from 2017 on.

Variables

Exposures

All antibiotics from the WHO AWaRe Reserve 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. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
2. Danish Data Health Registries (DK-DHR), Denmark
3. Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB–ULSEDV), Portugal
4. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
5. Papageorgiou General Hospital (PGH), Greece
6. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy
7. Semmelweis University Clinical Data (SUCD), Hungry

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 antibiotic 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 Reserve antibiotic category of the WHO AWaRe classification includes antibiotics considered last-resort treatments for confirmed or suspected infections caused by multidrug-resistant organisms. These antibiotics have a high resistance potential and should be used sparingly and only in specific, critical situations to preserve their effectiveness. 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, emphasizing the

need to limit the use of Reserve antibiotics. The Reserve category thus plays a vital role in supporting antimicrobial stewardship by guiding careful use, preventing overuse, and maintaining the efficacy of these critical agents in combating antimicrobial resistance.(13)

The aims of this study are to characterise the use of the prescribed antibiotics from Reserve category. This study will improve our understanding of the use of antibiotics in the Reserve 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 'Reserve' 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:	To investigate the incidence of prescription of individual antibiotics and antibiotics class (from the WHO AWaRe 'Reserve' 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 2012-2024, with at least 365 days of data availability (except hospitals data sources) before the day they become eligible for study inclusion. 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 'Reserve' 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 2012-2024 for the calculation of yearly/monthly incidence rates. 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 outpatient setting using data from the following data sources: CDWBordeaux (France), DK-DHR (Denmark), EMDB–

	ULSEDV (Portugal), IMASIS (Spain), PGH (Greece), POLIMI (Italy), SUCD (Hungry)
Main measure of effect:	Incidence rates of antibiotic use with 95% confidence intervals

A. Secondary objective 1.

Objective:	To characterise individual antibiotics and antibiotics class (WHO AWaRe 'Reserve' 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 (except hospitals data sources) 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 'Reserve' 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. 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:	Inpatient and/or outpatient setting using data from the following data sources: CDWBordeaux (France), DK-DHR (Denmark), EMDB–ULSEDV (Portugal), IMASIS (Spain), PGH (Greece), POLIMI (Italy), SUCD (Hungry)
Main measure of effect:	Duration of antibiotic use expressed as minimum, p25, median, p75, and maximum.

B. Secondary objective 2.

Objective:	To characterise individual antibiotic and antibiotics class (WHO AWaRe 'Reserve' 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 (except hospitals data

	sources) 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 'Reserve' 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. 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 7 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 'Reserve' 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 WHO AWaRe 'Reserve' category antibiotics utilisation in terms of duration and indication of use.

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

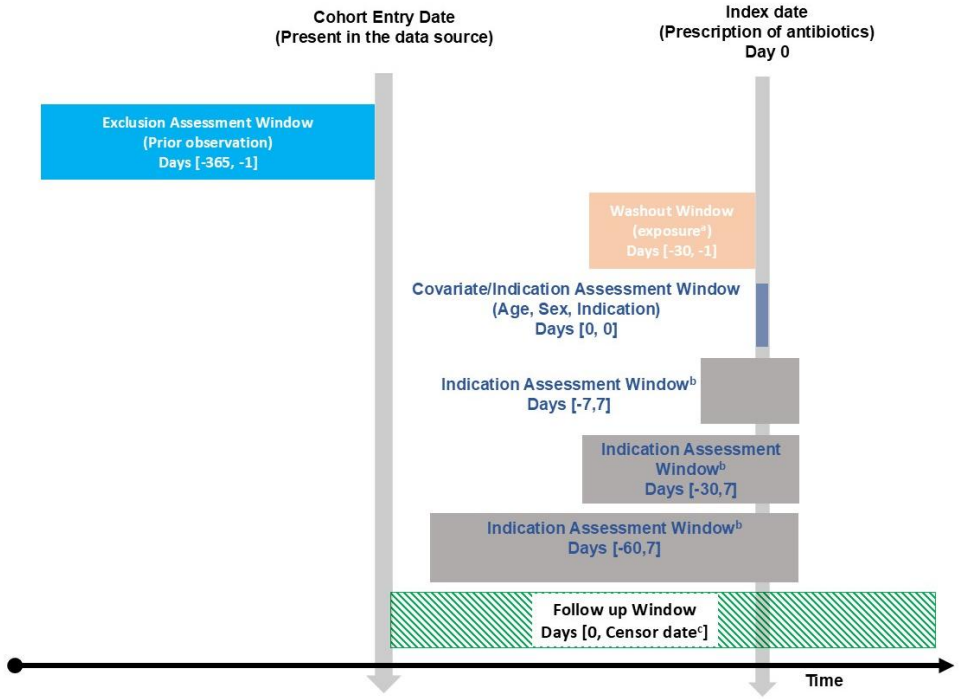


Figure 1. A graphical depiction of the study design.

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 7 primary/secondary care databases in the DARWIN EU® network of data partners from 7 European countries.

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
2. Danish Data Health Registries (DK-DHR), Denmark
3. Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB–ULSEDV), Portugal
4. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
5. Papageorgiou General Hospital (PGH), Greece
6. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy
7. Semmelweis University Clinical Data (SUCD), Hungry

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 (see Section D1.3.5.2 on Complete Data Quality Assurance Package) 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
France	CDWBordeaux	The data source includes inpatient hospital care and secondary outpatient care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of CDWBordeaux 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, other	246K	n/a	2024-02-22
Denmark	DK-DHR	The data source includes inpatient hospital care and secondary outpatient care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of DK-DHR contributes to geographical diversity of data sources included with adequate	Inpatient hospital care and secondary outpatient care	1, 2, and 3	EHRs, registries, other	5.98M	n/a	2025-4-10

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
		data availability over the study period.						
Portugal	EMDB–ULSEDV	The data source includes hospital inpatient care, hospital outpatient care, secondary special category care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of EMDB–ULSEDV contributes to geographical diversity of data sources included with adequate data availability over the study period.	Hospital inpatient care, hospital outpatient care, secondary care – specialist level (ambulatory)	1, 2, and 3	EHRs, other	95.4K	n/a	2023-11-01
Spain	IMASIS	The data source includes hospital inpatient and outpatient care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of IMASIS contributes to geographical diversity of data	Hospital inpatient care, hospital outpatient care, other	1, 2, and 3	EHRs, other	149K	n/a	2025-3-4

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
		sources included with adequate data availability over the study period.						
Greece	PGH	The data source includes primary care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of PGH contributes to geographical diversity of data sources included with adequate data availability over the study period.	Hospital inpatient care, hospital outpatient care, secondary care – specialist level (ambulatory)	1, 2, and 3	EHRs, other	2K	n/a	2025-5-3
Italy	POLIMI	The data source includes hospital inpatient care, hospital outpatient care, secondary specialist care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of POLIMI contributes to geographical diversity of data	Hospital inpatient care, hospital outpatient care, secondary care – specialist level (ambulatory)	1, 2, and 3	EHRs, other	89.1K	n/a	2022-02-14

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
		sources included with adequate data availability over the study period.						
Hungry	SUCD	The data source includes hospital inpatient care, hospital outpatient care, secondary specialist care where adequate number of patients exposed to the WHO AWaRe 'Reserve' category antibiotics and predefined medical conditions can be recorded. Use of SUCD contributes to geographical diversity of data sources included with adequate data availability over the study period.	Hospital inpatient care, hospital outpatient care, secondary care – specialist level (ambulatory)	1, 2, and 3	EHRs, other	212K	n/a	2025-01-22

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

CDWBordeaux= Clinical Data Warehouse of Bordeaux University Hospital; DK-DHR=Danish Data Health Registries; EMDB–ULSEDV= Egas Moniz Health Alliance database - Entre o Douro e Vouga; IMASIS= Institut Municipal Assistència Sanitària Information System; PGH= Papageorgiou General Hospital; POLIMI= Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; SUCD= Semmelweis University Clinical Data; EHR=Electronic Health Records; HER=Electronic Health Records

Bordeaux University Hospital (CHU Bordeaux), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).(18)

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).

Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB–ULSEDV), Portugal

The Clinical Academic Center Egas Moniz Health Alliance (CAC-EMHA) integrates several Portuguese institutions - the University of Aveiro and 4 Local Health Units (Aveiro, Entre Douro e Vouga, Vila Nova de Gaia/Espinho and Matosinhos). More than 1 million clinical records of patients are included. The CAC-EMHA has defined main problems for intervention, aligned with the needs of public health and considering the clinical and scientific differentiation of its professionals, in the following areas: a) cardiovascular and respiratory; b) muscle and bone; c) infection and resistance; d) neurosciences. Unidade Local de Saúde de Entre Douro e Vouga (ULSEDV) is an integrated public medical care centre comprising both primary, secondary and tertiary healthcare. It fully serves approximately 274.000 patients of the municipalities of Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva. The ULSEDV includes 32 primary care centres assisted by three hospitals (Hospital de São Sebastião, Hospital São João da Madeira, and Hospital São Miguel).

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, that are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM

and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Papageorgiou General Hospital (PGH), Greece

PGH, situated in Thessaloniki—the second-largest city in Greece—began operations in 1999. By 2004, it had formed a partnership with Aristotle University of Thessaloniki's School of Medicine, hosting its Teaching Clinics. The hospital boasts 30 clinics, including 2 Internal Medicine clinics, 2 Surgery clinics, 10 collaborative departments, and 8 laboratory centres. With a capacity of 745 beds, PGH employs 1.939 staff members and supports over 200,000 hospitalization days annually, conducts 20,000 surgeries, and manages approximately 1,000 daily visits to outpatient departments. The eHealth Lab at the Institute of Applied Biosciences, part of the Centre for Research and Technology Hellas (INAB|CERTH), focuses on developing software for medical informatics applications. INAB|CERTH, certified by EHDEN for its proficiency in Extract-Transform-Load (ETL) operations for OMOP-CDM, serves as a subcontractor managing PGH's OMOP-CDM instance on its behalf. PGH's information system integrates multiple databases—including Electronic Healthcare Records and Laboratory Information Systems—and aligns with international medical vocabularies and standards. It also encompasses an imaging system (PACS) to handle the extensive daily diagnostic imaging. Furthermore, PGH utilizes specialized software for logistical management, blood transfusion services, and more. The hospital's significant daily patient influx results in the production of a vast and diverse array of medical data.

Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy

Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, known simply as Policlinico of Milan, is a general hospital that can count on important excellence in different areas of care with a strong interdisciplinary focus. Given its nature as IRCCS – Institute for Research, Hospitalization and Health Care - in addition to care, it carries out biomedical and health research activities of a clinical and translational nature, involving the rapid transfer of therapies from the laboratories to the bedside of the sick person. The research activity is conducted in the different fields of medicine, from neurology to cardiology, from transplantation to haematology, to excellence of care in gynaecology, neonatology, geriatrics and rare diseases. Our DWH was born a few years ago with the aim of helping researchers in identifying patient cohorts and in obtaining large amounts of data for their studies more easily. A few years later, thanks to the EHDEN Project, we were also able to introduce the CDM OMOP. Currently the DWH contains data from Hospitalization, Outpatients visits, Laboratory test, Therapies, Radiology, Anatomic Pathology and a REDCap instance for non-profit studies.

Semmelweis University Clinical Data (SUCD), Hungry

Semmelweis University is the largest provider of health care services in Hungary. Most of the departments cater for the most serious cases and patients requiring complex treatment, thus making the university a national health care provider. The overwhelming majority of patient data originates from Hungary, mainly from central region of the country: Budapest and Pest County. The database contains approximately 2 million individual patients across all care settings of the University since 2011. The hospital information system (MedSolution) is an integrated IT system provides functional support for inpatient and outpatient care processes and serves as an integrated platform for different diagnostic areas, and in some specific area it supports the registration of medications. It supports all kinds of hospital work processes from admission to discharge. The outpatient module serves as a platform for the registration of activities related to care episode within the outpatient specialist care. During the care provision data related to health state of the patient, the diagnosis, the documentation of requested examinations and medical consultations, prescribed medication, final reports and performed interventions are recorded. The functions of the inpatient module

assist the care provision within the inpatient settings. It documents the health state of the patient at admission and during the hospital stay, along with the anamnesis, diagnosis, the performed examinations and interventions, hospital final reports and provided medication in some are of care provision such as chemotherapy. Among other modules the diagnostic module registers the requested laboratory and imaging examinations and records the laboratory results.

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 POLIMI data source, the availability of accurate data starts from 01 January 2017.

Since hospital records generally only cover the period from the first to the last visit, which may not fulfil the 365 days prior observation time requirement, patients from hospital data sources (CDW Bordeaux, IMASIS, SUCD, POLIMI, EMDB - ULSEDV, PGH) with less than 365 days of prior observation time will still be included in the analysis.

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.

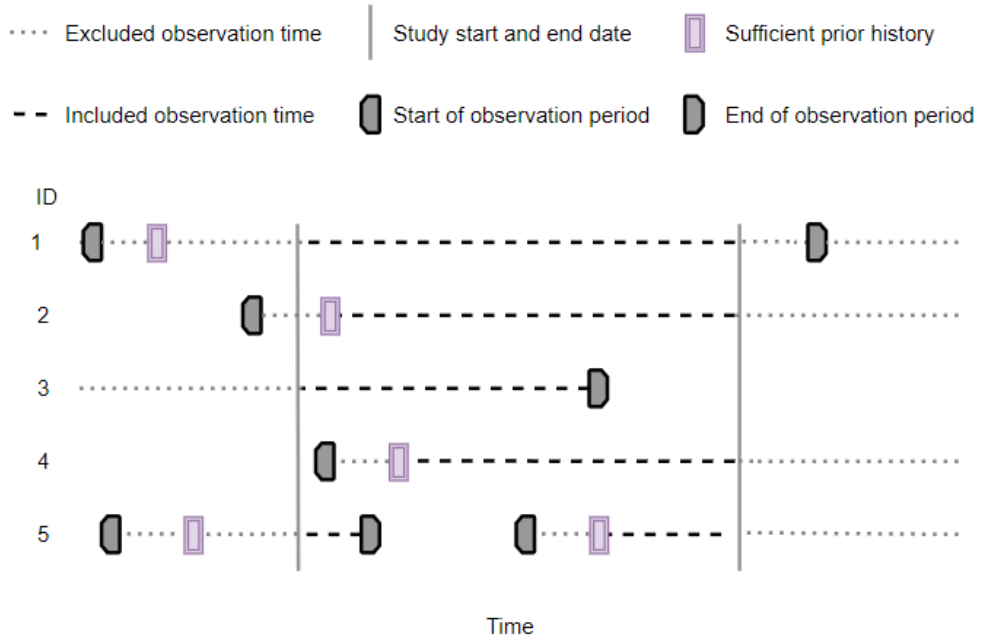


Figure 2. Included observation time for the denominator population.

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) and other primary time anchors.

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 and patients from hospitals data sources). 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 and patients from hospitals data sources).

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)	Before 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] OP = outpatient, OT = other, n/a = not applicable

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

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 'Reserve' category of the WHO 2023 AWaRe classification of antibiotics (who.int) (**Table 6**). The Reserve category represents critically important antibiotics with a high resistance potential, designated as last-resort treatments for severe infections caused by multidrug-resistant pathogens.

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

Antibiotics of Reserve category	Class	ATC code
Aztreonam	Monobactams	J01DF01
Carumonam	Monobactams	J01DF02
Cefiderocol	Other-cephalosporins	J01DI04
Ceftaroline-fosamil	Fifth-generation cephalosporins	J01DI02
Ceftazidime/avibactam	Third generation-cephalosporins	J01DD52
Ceftobiprole-medocaril	Fifth generation cephalosporins	J01DI01
Ceftolozane/tazobactam	Fifth generation cephalosporins	J01DI54
Colistin_IV	Polymyxins	J01XB01
Colistin_oral	Polymyxins	A07AA10
Dalbavancin	Glycopeptides	J01XA04
Dalfopristin/quinupristin	Streptogramins	J01FG02
Daptomycin	Lipopeptides	J01XX09
Eravacycline	Tetracyclines	J01AA13
Faropenem	Penems	J01DI03
Fosfomycin_IV	Phosphonics	J01XX01
Iclaprim	Trimethoprim-derivatives	J01EA03
Imipenem/cilastatin/relebact	Carbapenems	J01DH56
Lefamulin	Pleuromutilin	J01XX12
Linezolid	Oxazolidinones	J01XX08
Meropenem/vaborbactam	Carbapenems	J01DH52
Minocycline_IV	Tetracyclines	J01AA08
Omadacycline	Tetracyclines	J01AA15
Oritavancin	Glycopeptides	J01XA05
Plazomicin	Aminoglycosides	J01GB14
Polymyxin-B_IV	Polymyxins	J01XB02
Polymyxin-B_oral	Polymyxins	A07AA05
Tedizolid	Oxazolidinones	J01XX11
Telavancin	Glycopeptides	J01XA03
Tigecycline	Glycylcyclines	J01AA12

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 class) 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 "Reserve" category of the WHO 2023 AWaRe classification	Preliminary codes list 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 with 10-year age bands namely: 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 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 antibiotics use from WHO AWaRe Reserve category. They will be assessed 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 Reserve 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®(19, 20) 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.

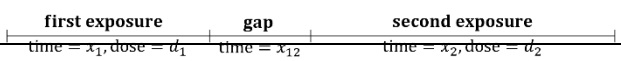
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		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 the prescription (exception for children <1 year and patients from hospitals data sources). 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 index date of the respective drug (index date) [primary definition] or during assessment windows within +/-7 days, -30 - +7 days, and -60 - +7 days of the index date [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.

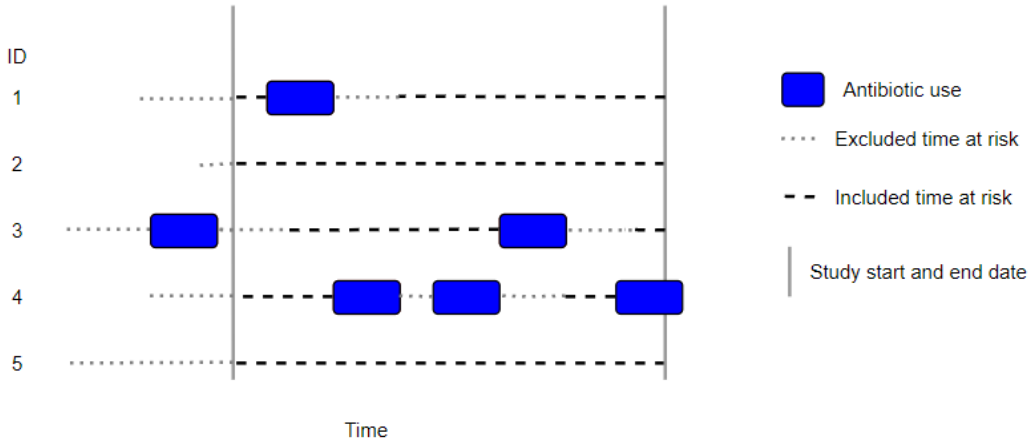


Figure 4. Incidence examples for antibiotic use.

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 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 incident prescription. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration.

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 table(s) and figure(s):

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 'Reserve' category*.

Antibiotic name	Characteristic	CDWBordeaux	DK-DHR	EMDB–ULSEDV	IMASIS	PGH	POLIMI	SUCD
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 'Reserve' category*

Table shell. Overall incidence rates per 100,000 PYs (95% confidence intervals) of antibiotics from the WHO AWaRe 'Reserve' category – 10 most prescribed antibiotics across data sources of CDWBordeaux, DK-DHR, EMDB–ULSEDV, IMASIS, PGH, POLIMI, and SUCD over years 2012-2024.

CDWBordeaux		DK-DHR		EMDB–ULSEDV		IMASIS		PGH		POLIMI		SUCD	
Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)	Antibiotic name	Incidence rates (95% CI)

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

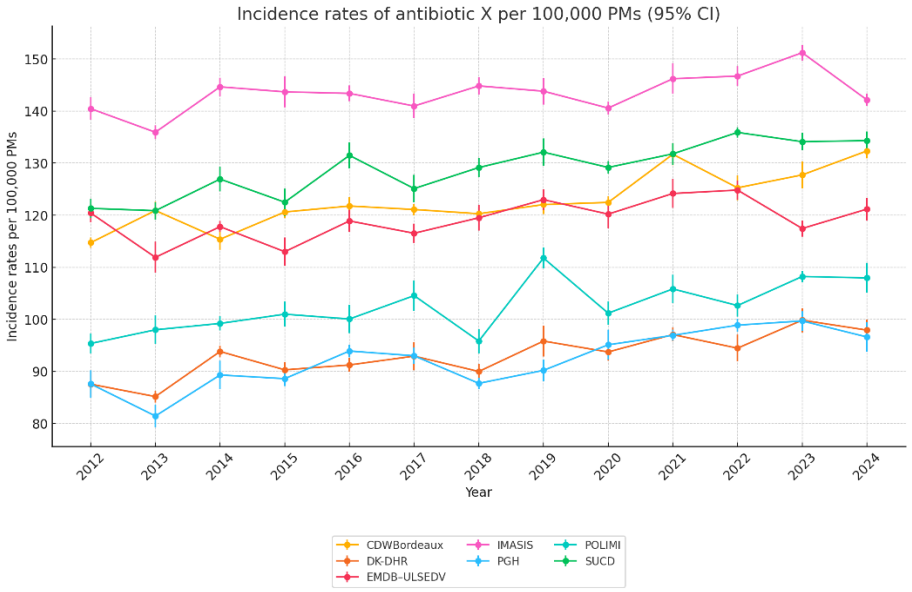


Figure templates (one for each 10 most prescribed antibiotics across data sources). Overall yearly incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources CDWBordeaux, DK-DHR, EMDB–ULSEDV, IMASIS, PGH, POLIMI, and SUCD over years 2012-2024. (The use of coloured lines 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 Template of this section below.

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

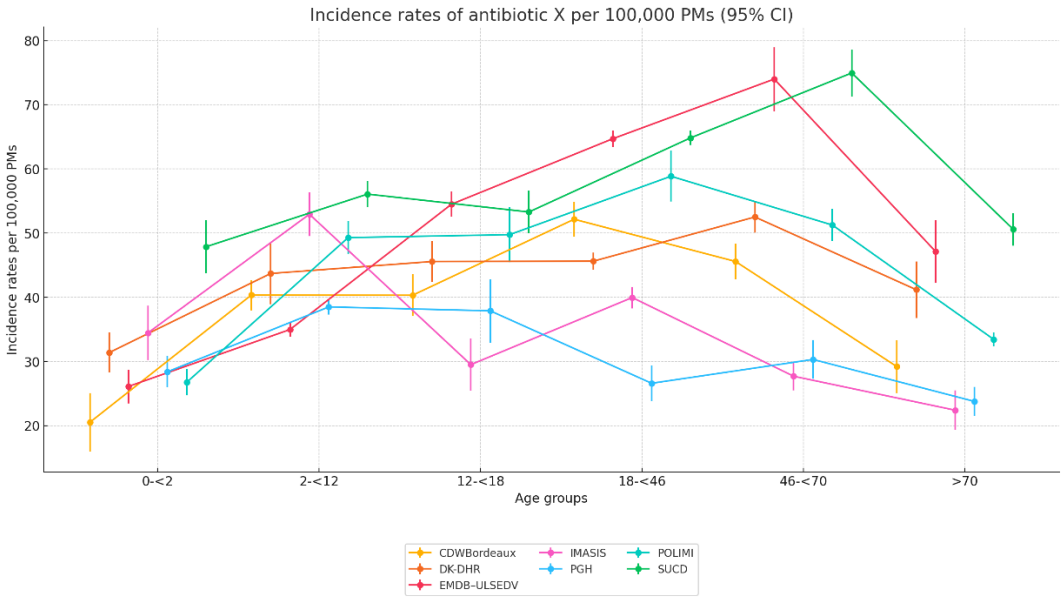


Figure templates (one for each 10 most prescribed antibiotics across data sources). Incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources CDWBordeaux, DK-DHR, EMDB–ULSEDV, IMASIS, PGH, POLIMI, and SUCD stratified by age group (The use of coloured lines in the visualizations will reflect the underlying data settings).

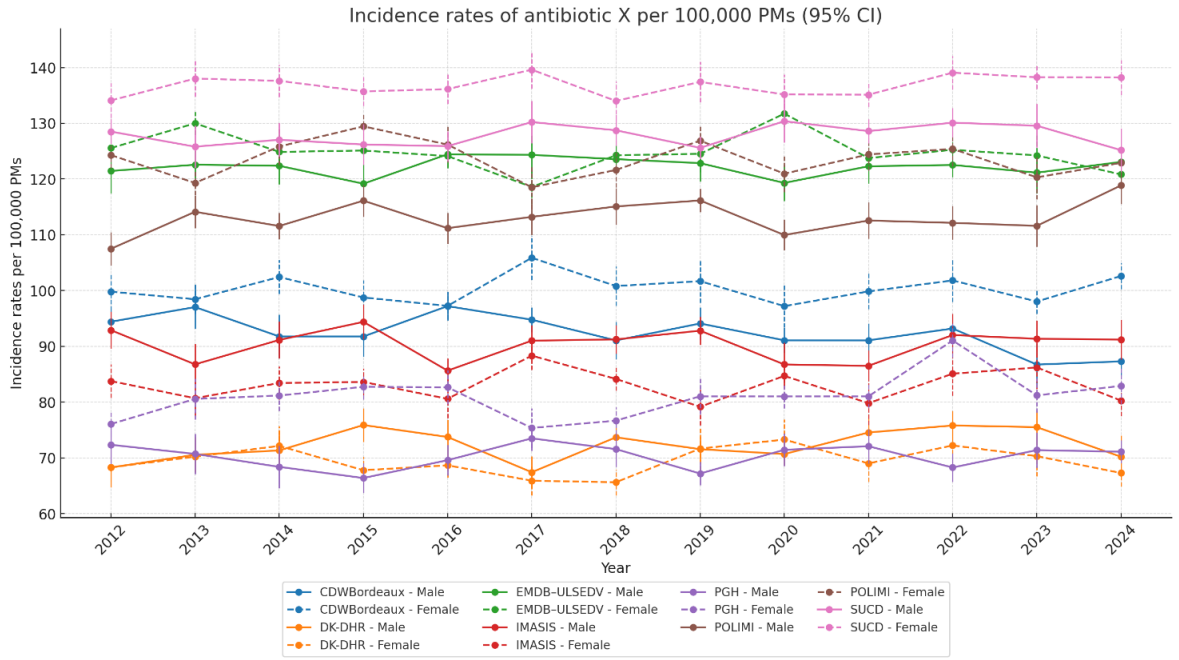


Figure templates (one for each 10 most prescribed antibiotics across data sources). Incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources CDWBordeaux, DK-DHR, EMDB–ULSEDV, IMASIS, PGH, POLIMI, and SUCD stratified by sex.

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 'Reserve' category –10 most prescribed across data sources.

	CDWBordeaux	DK-DHR	EMDB–ULSEDV	IMASIS	PGH	POLIMI	SUCD
Antibiotic 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)	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 from the WHO AWaRe 'Reserve' 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 'Reserve' category.

	CDWBordeaux	DK-DHR	EMDB–ULSEDV	IMASIS	PGH	POLIMI	SUCD
	Antibiotic name						
N overall							
condition 1 [n (%)]							
condition 2 [n (%)]							
condition 3 [n (%)]							
condition 4 [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.

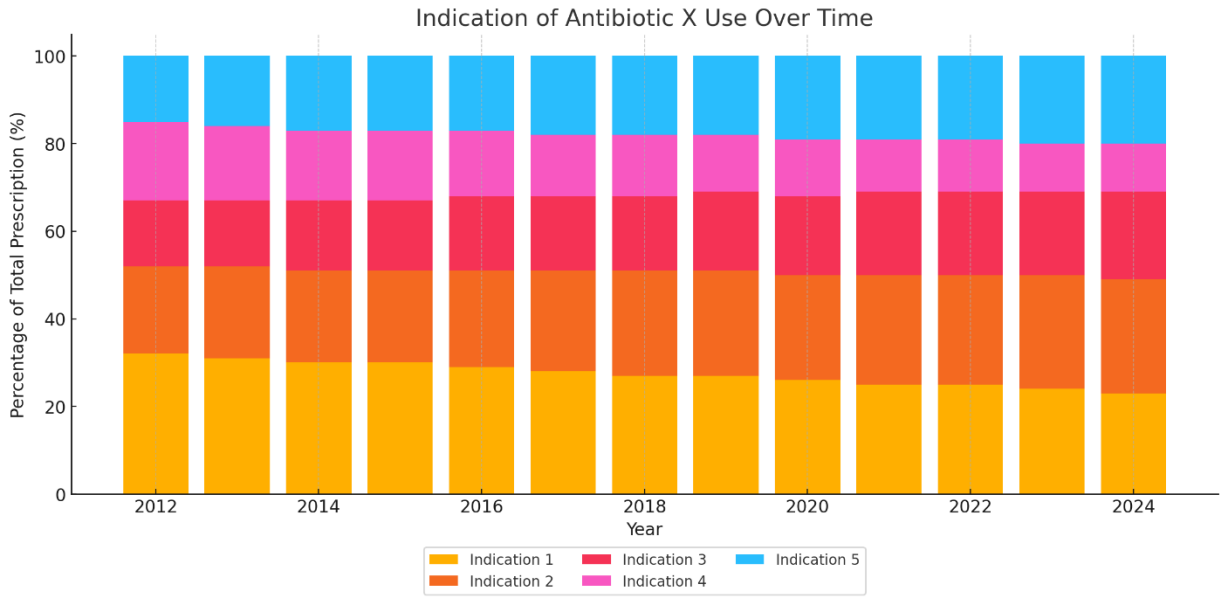


Figure templates (one for each 10 most prescribed antibiotics across data sources). Trends in the indications for prescribing Antibiotic X in (data source name) during the study period 2012–2024.

APPENDIX RESULTS

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

		CDWBordeaux		DK-DHR		EMDB–ULSEDV		IMASIS		PGH		POLIMI		SUCD	
Steps	Reasons	Current_n	Excluded	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)														

		CDWBordeaux		DK-DHR		EMDB–ULSEDV		IMASIS		PGH		POLIMI		SUCD	
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 'Reserve' 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)**

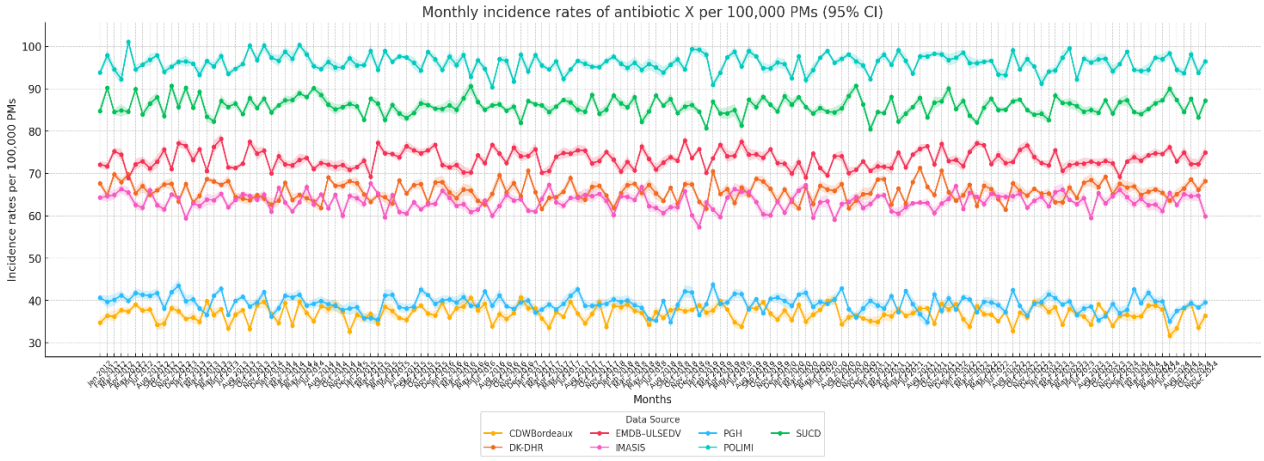


Figure templates S (one for each 10 most prescribed antibiotics across data sources). Monthly incidence rates per 100,000 PYs (95% confidence intervals) of antibiotic X in data sources CDWBordeaux, DK-DHR, EMDB–ULSEDV, IMASIS, PGH, POLIMI, and SUCD over years 2012-2024 (The use of coloured lines in the 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 'Reserve' category.

	CDWBordeaux	DK-DHR	EMDB–ULSEDV	IMASIS	PGH	POLIMI	SUCD
	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 'Reserve' category per data source (in windows around index date: [-7, 7] and [-30, 7])

	CDWBordeaux		DK-DHR		EMDB–ULSEDV		IMASIS		PGH		POLIMI		SUCD	
	Antibiotic name													
N overall	N		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]	[-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		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 DPs 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 performed 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.

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.

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 the France, Spain, Denmark, Hungary, Italy, Portugal, Greece 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 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. ANNEXES

Appendix I: Concepts set for study variables

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

Table S1. Preliminary list of concept IDs for antibiotics from WHO AWaRe 'Reserve' category exposure definition.

	Antibiotics of Reserve category	Class	ATC code	Concept id (including descendants)	Concept Name	vocabulary
1	Aztreonam	Monobactams	J01DF01	21602919	Aztreonam	RxNorm
2	Carumonam	Monobactams	J01DF02	40255589	Carumonam	RxNorm
3	Cefiderocol	Other-cephalosporins	J01DI04	947954	Cefiderocol	RxNorm
4	Ceftaroline-fosamil	Fifth-generation cephalosporins	J01DI02	40255830	Ceftaroline fosamil	RxNorm
5	Ceftazidime/avibactam	Third generation-cephalosporins	J01DD52	1588654	Ceftazidime/avibactam	RxNorm
6	Ceftobiprole-medocaril	Fifth generation cephalosporins	J01DI01	21602928	Ceftobiprole medocaril	RxNorm
7	Ceftolozane/tazobactam	Fifth generation cephalosporins	J01DI54	1588709	Ceftolozane/tazobactam	RxNorm
8	Colistin_IV	Polymyxins	J01XB01	21603049	Colistin	RxNorm
9	Colistin_oral	Polymyxins	A07AA10	21600612	Colistin	RxNorm
10	Dalbavancin	Glycopeptides	J01XA04	21603046	Dalbavancin	RxNorm
11	Dalfopristin/quinupristin	Streptogramins	J01FG02	21602989	Dalfopristin/quinupristin	RxNorm
12	Daptomycin	Lipopeptides	J01XX09	21603069	Daptomycin	RxNorm
13	Eravacycline	Tetracyclines	J01AA13	715903	Eravacycline	RxNorm
14	Faropenem	Penems	J01DI03	43534793	Faropenem	RxNorm
15	Fosfomycin_IV	Phosphonics	J01XX01	21603061	Fosfomycin	RxNorm
16	Iclaprim	Trimethoprim-derivatives	J01EA03	21602933	Iclaprim	RxNorm
17	Imipenem/cilastatin/relebactam	Carbapenems	J01DH56	947871	Imipenem/ cilastatin/relebactam	RxNorm
18	Lefamulin	Pleuromutilin	J01XX12	715839	Lefamulin	RxNorm
19	Linezolid	Oxazolidinones	J01XX08	21603068	Linezolid	RxNorm
20	Meropenem/vaborbactam	Carbapenems	J01DH52	715909	Meropenem/vaborbactam	RxNorm

21	Minocycline_IV	Tetracyclines	J01AA08	21602806	Minocycline	RxNorm
22	Omadacycline	Tetracyclines	J01AA15	715905	Omadacycline	RxNorm
23	Oritavancin	Glycopeptides	J01XA05	21603047	Oritavancin	RxNorm
24	Plazomicin	Aminoglycosides	J01GB14	715795	Plazomicin	RxNorm
25	Polymyxin-B_IV	Polymyxins	J01XB02	21603050	Polymyxin-B	RxNorm
26	Polymyxin-B_oral	Polymyxins	A07AA05	21600607	Polymyxin-B	RxNorm
27	Tedizolid	Oxazolidinones	J01XX11	1588637	Tedizolid	RxNorm
28	Telavancin	Glycopeptides	J01XA03	21603045	Telavancin	RxNorm
29	Tigecycline	Glycylcyclines	J01AA12	21602810	Tigecycline	RxNorm

*Non-systemic antibiotics will be excluded.

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 exacerbation of chronic obstructive pulmonary disease	-	SNOMED

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
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 infection in pregnancy, Renal abscess, Renal and perinephric abscess	42600293, 42598600, 42593547, 42598968, 42573007, 42600389, 42572888, 3194810, 4056622, 4047937, 607157, 4032450, 42600089, 4100954, 606982, 4239213, 4030507, 37017585, 4128374, 37017217, 954561	SNOMED

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
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, 42597228, 42597288, 42597289, 42597232, 42574047, 42597209, 42597155	SNOMED
Septic arthritis	4180167	Infectious disorder of joint	42598859, 42599075, 42598482, 42597189, 42598680, 42573193, 42598483, 42597162, 42597218, 42597169, 42574034, 42599633,	SNOMED

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
			42597196, 42597291, 42597269, 42598723, 42599281, 42597284, 42574047, 42575811	
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, 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,	SNOMED

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
			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, 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,	

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
			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, 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

Phenotypes	Concept IDs (including descendants) *	Concept names	Exclude concept IDs	Vocabulary
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.

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 'Reserve' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use

EU PAS Register® number: EUPAS1000000664
Study reference number (if applicable): P3-C1-023

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:

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:

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:

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:

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:

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
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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:

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?	☒	☐	☐	8.8
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:

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:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias?	☒	☐	☐	

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

Comments:

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:

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:

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: