Study Report C1-003

27th March 2023

Version 3.1

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Document History

Version	Date	Description
V1.0	23/01/2023	**First Version for EMA review**
V2.0	06/02/2023	**Second Version for EMA review**
V3.0	15/02/2023	**Final version incorporating EMA comments**
V3.1	27/03/2023	**Link to Shiny App added**

Study Title	DARWIN EU® - Drug Utilisation Study of Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.		
Study Report Version identifier	V3.1		
Dates Study Report updates	NA		
EU PAS register number	EUPAS103381		
Active substance per the WHO AWare list (1)	**Antibiotic**	**Class**	**ATC code**
	Arbekacin	Aminoglycosides	J01GB12
	Aspoxicillin	Penicillins	J01CA19
	Azithromycin	Macrolides	J01FA10
	Azlocillin	Penicillins	J01CA09
	Bekanamycin	Aminoglycosides	J01GB13
	Biapenem	Carbapenems	J01DH05
	Carbenicillin	Penicillins	J01CA03
	Carindacillin	Penicillins	J01CA05
	Cefaclor	Second-generation	J01DC04
	Cefamandole	Second-generation	J01DC03
	Cefbuperazone	Second-generation	J01DC13
	Cefcapene-pivoxil	Third-generation	J01DD17
	Cefdinir	Third-generation	J01DD15
	Cefditoren-pivoxil	Third-generation	J01DD16
	Cefepime	Fourth-generation	J01DE01
	Cefetamet-pivoxil	Third-generation	J01DD10
	Cefixime	Third-generation	J01DD08
	Cefmenoxime	Third-generation	J01DD05
	Cefmetazole	Second-generation	J01DC09
	Cefminox	Second-generation	J01DC12
	Cefodizime	Third-generation	J01DD09
	Cefonicid	Second-generation	J01DC06
	Cefoperazone	Third-generation	J01DD12
	Ceforanide	Second-generation	J01DC11
	Cefoselis	Fourth-generation	to be assigned
	Cefotaxime	Third-generation	J01DD01
	Cefotetan	Second-generation	J01DC05
	Cefotiam	Second-generation	J01DC07
	Cefoxitin	Second-generation	J01DC01
	Cefozopran	Fourth-generation	J01DE03
	Cefpiramide	Third-generation	J01DD11

	Cefpirome	Fourth-generation	J01DE02
	Cefpodoxime-proxetil	Third-generation	J01DD13
	Cefprozil	Second-generation	J01DC10
	Cefsulodin	Third-generation	J01DD03
	Ceftazidime	Third-generation	J01DD02
	Cefteram-pivoxil	Third-generation	J01DD18
	Ceftibuten	Third-generation	J01DD14
	Ceftizoxime	Third-generation	J01DD07
	Ceftriaxone	Third-generation	J01DD04
	Cefuroxime	Second-generation	J01DC02
	Chlortetracycline	Tetracyclines	J01AA03
	Cinoxacin	Quinolones	J01MB06
	Ciprofloxacin	Fluoroquinolones	J01MA02
	Clarithromycin	Macrolides	J01FA09
	Clofoctol	Phenol derivatives	J01XX03
	Clomocycline	Tetracyclines	J01AA11
	Delafloxacin	Fluoroquinolones	J01MA23
	Demeclocycline	Tetracyclines	J01AA01
	Dibekacin	Aminoglycosides	J01GB09
	Dirithromycin	Macrolides	J01FA13
	Doripenem	Carbapenems	J01DH04
	Enoxacin	Fluoroquinolones	J01MA04
	Ertapenem	Carbapenems	J01DH03
	Erythromycin	Macrolides	J01FA01
	Fidaxomicin	Macrolides	A07AA12
	Fleroxacin	Fluoroquinolones	J01MA08
	Flomoxef	Second-generation	J01DC14
	Flumequine	Quinolones	J01MB07
	Flurithromycin	Macrolides	J01FA14
	Fosfomycin_oral	Phosphonics	J01XX01
	Fusidic-acid	Steroid antibacterials	J01XC01
	Garenoxacin	Fluoroquinolones	J01MA19
	Gatifloxacin	Fluoroquinolones	J01MA16
	Gemifloxacin	Fluoroquinolones	J01MA15
	Grepafloxacin	Fluoroquinolones	J01MA11
	Imipenem/cilastatin	Carbapenems	J01DH51
	Isepamicin	Aminoglycosides	J01GB11
	Josamycin	Macrolides	J01FA07
	Kanamycin_IV	Aminoglycosides	J01GB04
	Kanamycin_oral	Aminoglycosides	A07AA08
	Lascufloxacin	Fluoroquinolones	J01MA25
	Latamoxef	Third-generation	J01DD06
	Levofloxacin	Fluoroquinolones	J01MA12

	Levonadifloxacin	Fluoroquinolones	J01MA24
	Lincomycin	Lincosamides	J01FF02
	Lomefloxacin	Fluoroquinolones	J01MA07
	Loracarbef	Second-generation	J01DC08
	Lymecycline	Tetracyclines	J01AA04
	Meropenem	Carbapenems	J01DH02
	Metacycline	Tetracyclines	J01AA05
	Mezlocillin	Penicillins	J01CA10
	Micronomicin	Aminoglycosides	to be assigned
	Midecamycin	Macrolides	J01FA03
	Minocycline_oral	Tetracyclines	J01AA08
	Miocamycin	Macrolides	J01FA11
	Moxifloxacin	Fluoroquinolones	J01MA14
	Nemonoxacin	Quinolones	J01MB08
	Neomycin_IV	Aminoglycosides	J01GB05
	Neomycin_oral	Aminoglycosides	A07AA01
	Netilmicin	Aminoglycosides	J01GB07
	Norfloxacin	Fluoroquinolones	J01MA06
	Ofloxacin	Fluoroquinolones	J01MA01
	Oleandomycin	Macrolides	J01FA05
	Oxolinic-acid	Quinolones	J01MB05
	Oxytetracycline	Tetracyclines	J01AA06
	Panipenem	Carbapenems	J01DH55
	Pazufloxacin	Fluoroquinolones	J01MA18
	Pefloxacin	Fluoroquinolones	J01MA03
	Penimepicycline	Tetracyclines	J01AA10
	Pheneticillin	Penicillins	J01CE05
	Pipemidic-acid	Quinolones	J01MB04
	Piperacillin	Penicillins	J01CA12
	Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05
	Piromidic-acid	Quinolones	J01MB03
	Pristinamycin	Streptogramins	J01FG01
	Prulifloxacin	Fluoroquinolones	J01MA17
	Ribostamycin	Aminoglycosides	J01GB10
	Rifabutin	Rifamycins	J04AB04
	Rifampicin	Rifamycins	J04AB02
	Rifamycin_IV	Rifamycins	J04AB03
	Rifamycin_oral	Rifamycins	A07AA13
	Rifaximin	Rifamycins	A07AA11
	Rokitamycin	Macrolides	J01FA12
	Rolitetracycline	Tetracyclines	J01AA09
	Rosoxacin	Quinolones	J01MB01

	Roxithromycin	Macrolides	J01FA06
	Rufloxacin	Fluoroquinolones	J01MA10
	Sarecycline	Tetracyclines	J01AA14
	Sisomicin	Aminoglycosides	J01GB08
	Sitafloxacin	Fluoroquinolones	J01MA21
	Solithromycin	Macrolides	J01FA16
	Sparfloxacin	Fluoroquinolones	J01MA09
	Spiramycin	Macrolides	J01FA02
	Streptoduocin	Aminoglycosides	J01GA02
	Streptomycin_IV	Aminoglycosides	J01GA01
	Streptomycin_oral	Aminoglycosides	A07AA04
	Sulbenicillin	Penicillins	J01CA16
	Tazobactam	Beta-lactamase-inhibitors	J01CG02
	Tebipenem	Carbapenems	J01DH06
	Teicoplanin	Glycopeptides	J01XA02
	Telithromycin	Macrolides	J01FA15
	Temafloxacin	Fluoroquinolones	J01MA05
	Temocillin	Penicillins	J01CA17
	Ticarcillin	Penicillins	J01CA13
	Tobramycin	Aminoglycosides	J01GB01
	Tosufloxacin	Fluoroquinolones	J01MA22
	Troleandomycin	Macrolides	J01FA08
	Trovafloxacin	Fluoroquinolones	J01MA13
	Vancomycin_IV	Glycopeptides	J01XA01
	Vancomycin_oral	Glycopeptides	A07AA09
Medicinal product	NA		
Research question and objectives	This study aimed to characterise the incidence of prescription of the 141 antibiotics in the 'Watch' list, including indication and treatment duration, for the period 2012-2021, stratified by year and country.		
Country(-ies) of study	The Netherlands, France, Spain, Germany and the UK.		
Author(s)	Katia Verhamme Maria de Ridder		

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Study Project Manager/Principal Investigator	Katia Verhamme Maria de Ridder	Erasmus MC
Data Scientist	Marti Catala Sabate	University of Oxford
Epidemiologist	Annika Jodicke	University of Oxford
Statistician	Maria de Ridder	Erasmus MC
Data Manager	Mees Mosseveld	Erasmus MC
Data Partner*	**Names**	**Organisation**
Data Partner(s)	Antonella Delmestri Hezekiah Omulo Mees Mosseveld Hanne van Ballegooijen Miguel-Angel Mayer Romain Griffier / Vianney Jouhet Talita Duarte Salles	University of Oxford – CPRD data University of Oxford – CPRD data Erasmus MC – IPCI data IQVIA LPD/IQVIA Germany PSMAR – IMASIS data CHUBX IDIAPJGol – SIDIAP data

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

2. DATA SOURCES

This study was conducted using routinely collected data from 6 databases in 5 European countries (4 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Bordeaux University Hospital (CHUBX), France
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Parc Salut Mar Barcelona, Hospital del Mar (IMASIS) (hospital database), Spain
5. IQVIA Disease Analyzer Germany (IQVIA Germany), Germany
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Detailed information on data source is described below.

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of subjects in database	End of calendar period covered
NL	IPCI	Primary care	EHR	2.7 million	30/6/2022
FR	CHUBX	Secondary care (in and outpatients)	EHR	2.2 million	18/12/2022
ES	SIDIAP	Primary care	EHR	8.3 million	30/6/2022
ES	IMASIS	Secondary care (in and outpatients)	EHR	1.0 million	9/7/2022
DE	IQVIA Germany	Primary care and outpatient specialist care	EHR	8.5 million	30/6/2022
UK	CPRD GOLD	Primary care	EHR	15.7 million	30/6/2020

NL = The Netherlands, FR= France, ES = Spain, DE = Germany, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; CHUBX= Bordeaux University Hospital, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS= Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription/dispensing data

3. ABSTRACT

Title

DARWIN EU® - Drug Utilisation Study (DUS) of Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.

Rationale and Background

The WHO 2021 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 "Watch list" includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring.

With this study we aimed to improve our understanding of the use of antibiotics from the Watch category in routine health care delivery, including indication, treatment duration and trends over time in 5 European countries (4 EU countries and United Kingdom). Our 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

The objectives of this study were

1. To investigate the incidence rate and prevalence of use of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021.
2. To explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on antibiotics)
- New drug user cohort study (Objective 2, Patient-level drug utilisation analysis with regard to duration and indication of antibiotic use)

Population

Population-level utilisation of antibiotics: All individuals present in the database in the period between 01/01/2012 and 31/12/2021 were included in the analysis after 365 days of database history. For this population, the prevalence and incidence of use of antibiotics was explored.

Patient-level antibiotic utilisation: All new users of antibiotics after not using the antibiotic of interest for 30 days in the period between 01/01/2012 and 31/12/2021, with at least 365 days of visibility prior to the date of their first antibiotic prescription/dispensing.

Variables

Substances of interest: All antibiotics from the WHO Watch list

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Bordeaux University Hospital (CHUBX), France
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Parc Salut Mar Barcelona, Hospital del Mar (IMASIS) (hospital database), Spain
5. IQVIA Disease Analyzer Germany (IQVIA Germany), Germany (data not yet included in this report)
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Sample size

No sample size has been calculated. Prior to study initiation, feasibility counts were generated in the general population in each database.

Data analyses

Population-level antibiotic use: Annual period prevalence of antibiotic use and annual incidence rates per 100,000 person years. Stratification of incidence and prevalence numbers by sex and age group was provided for the antibiotic subclasses and not by individual antibiotic.

Patient-level antibiotic use: Large-scale patient-level characterisation was conducted. Index date was the date of the first prescription/dispensing of the specific antibiotic for each person. The frequency of indication of use was assessed by searching for disease codes belonging to predefined infectious disease categories. Besides, for each specific antibiotic, the top 10 of SNOMED codes reported at index date was determined. The treatment duration per drug era (= which was the combination of adjacent prescriptions) was calculated and the minimum, p25, median, mean, p75, and maximum were provided.

For all analyses a minimum cell count of 5 was used when reporting results. If the number of individuals within a cell was <5, counts were suppressed.

Results

Population-level utilisation of antbiotics

Although the list of antibiotics from the WHO Watch list is extensive (137 individual ingredients) only 78 of these were prescribed in at least one of the data sources during the study period. Of the prescribed antibiotics, few had an incidence rate > 100/100,000 person-years (PY) (6 antibiotics in CPRD GOLD, 9 in IPCI, 10 in SIDIAP, 12 in IMASIS, 7 in CHUBX and 14 in IQVIA Germany). Those antibiotics with the highest incidence rates were the same within the databases with, for instance, high prescribing (amongst top 3) of ciprofloxacin in all 4 primary care databases. Other drugs frequently prescribed in primary care were clarithromycin (CPRD GOLD and IPCI), fosfomycin (IPCI, SIDIAP and IQVIA Germany) and azithromycin (IPCI, SIDIAP and IQVIA Germany). In secondary care, higher use of ceftriaxone, vancomycin and meropenem was observed, which are drugs usually prescribed in secondary care.

An increase in incidence rate over time was observed for ceftriaxone (IMASIS and CHUBX), cefuroxime (SIDIAP and IMASIS), piperacilline-tazobactam (CHUBX) and vancomycin (IMASIS). For azithromycin, different patterns were observed by database with an increase in IMASIS and SIDIAP up to 2018 and 2020 respectively, a decrease in IPCI and stable use in CPRD GOLD and CHUBX. A decrease or steady state in incidence rate was observed for the fluoroquinolones. Other antibiotics for which the incidence rate clearly decreased over time were pheneticillin (IPCI), oxytetracycline (CPRD GOLD), erythromycin (CPRD GOLD) and clarithromycin (CPRD GOLD).

Antibiotic use was lower in children than in adults and use increased with increasing age. For some of the antibiotics, use was also high in children or young adults such as macrolides, second generation cephalosporins and tetracyclines.

Use of antibiotics was comparable in males compared to females except for Beta lactamase-inhibitor_anti-pseudomonal antibiotics (i.e. Piperacillin/tazobactam), carbapenem and 4th generation cephalosporins where use was higher in males than in females. For phosphonics, the opposite was observed with higher use in females.

The prevalence of antibiotic use mirrored the results of the incidence rates with highest use for azithromycin (especially in SIDIAP), ciprofloxacin, clarithromycin and fosfomycin.

Patient-level antibiotic utilisation:

In primary care databases, the median duration of an antibiotic exposure period ranged around a week except for fosfomycin where median duration was around 1 day. The median duration of antibiotic use was shorter in hospital databases (IMASIS and CHUBX) compared to primary care databases.

With regard to the indication of use, the proportion of prescriptions/dispensing where either the indication is unknown (i.e. presence of a disease code but not belonging to any of the infection classes that had been generated) or the indication is missing (no disease code around the prescription/dispensing) is high. E.g. for ciprofloxacin proportions with no indication were between 3% and 47%, proportion with only indication outside the predefined classes between 29% and 80%.

Exploring the top 10 of disease codes reported at the time of the prescription date (i.e. index date), proved to be informative as these conditions often referred to infections (some of which were not included amongst the concept codes to define the different categories of infections).

Discussion

Of the list of antibiotics from the WHO Watch list (137 individual substances), exposure to any of these drugs was reported for 78 antibiotics of this list. Incidence rate were mainly below 100/100.000 PY except for use of ciprofloxacin, clarithromycin, fosfomycin and azithromycin in most of the databases. The incidence rate remained stable or decreased over time except for ceftriaxone, cefuroxime, piperacillin-tazobactam and vancomycin that are mainly prescribed in secondary care. For the majority of investigated antibiotics, the incidence increased with age and was comparable by sex. The median duration of use was usually around one week but shorter in secondary care. If available, disease codes can provide valuable information on the indication of use.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
IMASIS	Institut Municipal Assistència Sanitària Information System
IPCI	Integrated Primary Care Information Project
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PSMAR	Parc de Salut Mar Barcelona
PY	Person Years
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
NA				

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Final Study Protocol	30/11/2022	30/11/2022
Creation of Analytical code	09/2022-12/2022	
Execution of Analytical Code on the data	01/2023	01/2023
Interim Study Report (if applicable)	NA	NA
Final Study Report	23rd January 2023	23rd January 2023
Revised Study Report		6th February 2023
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7. RATIONALE AND BACKGROUND

Bacterial infections are a major cause of morbidity and mortality worldwide. (2) Antibiotics have been hugely successful in improving health outcomes, and alongside improvements in nutrition, clean water, sanitation, and vaccination provision, have aided in the global reduction of mortality below the age of 5 years from 216 deaths per 1,000 livebirths in 1950 to 39 deaths per 1,000 livebirths in 2017, and an increase in male life expectancy from 48 years to 71 years within the same time period. (3, 4)

Antibiotics play a crucial role in the treatment of infections caused by bacteria but one of the greatest concerns is the risk of resistance. (5) To improve the appropriate use of antibiotics, Antibiotic Stewardship programs have been implemented with the aim to monitor the use of antibiotics and ensure that guidelines on the use of antibiotics are strictly adhered to. (6)

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 antibiotic stewardship 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. (7) The 2021 update of the AWaRe classification includes an additional 78 antibiotics not previously classified, bringing the total to 258.

The Watch list includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential Medicines.

The AWARe classification is a useful tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance. The WHO 13th General Programme of Work 2019–2023 includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics.

This study will improve our understanding of the use of antibiotics in the Watch 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.

8. RESEARCH QUESTION AND OBJECTIVES

This study addressed the following objectives:

1. To investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021.
2. To explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing.

Table 8.1: Primary research question and objective.

Objective:	To investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021
Hypothesis:	Not applicable

Population *(mention key inclusion-exclusion criteria):*	The study cohort comprised all individuals present in the database in the period 2012-2021, with at least 365 days of data availability before the day they became eligible for study inclusion. Additional eligibility criteria were applied for the calculation of incidence rates where observation time during the respective use of the antibiotic of interest was excluded during use and 30 days afterwards.
Exposure:	Antibiotics from the WHO Watch list.
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2021 for the calculation of annual incidence/prevalence rates. End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2021)
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (NL), CHUBX (France), SIDIAP (Spain), IMASIS (Spain), IQVIA (Germany) and CPRD GOLD (UK)
Main measure of effect:	Incidence and prevalence of antibiotic use

Table 8.2: Secondary research question and objective.

Objective:	To characterize antibiotic use in terms of duration and indication of use.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study cohort comprised all individuals present in the database in the period 2012-2021 (or the latest available), with at least 365 days of data availability before the day they became eligible for study inclusion and who had received at least one prescription and/or dispensing of one of the antibiotics of interest after not using the specific antibiotic for 30 days during the study period.
Exposure:	Antibiotics from the WHO Watch list.
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2021 for the calculation of annual incidence/prevalence rates.

	End of follow-up was defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2021)
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (NL), CHUBX (France), SIDIAP (Spain), IMASIS (Spain), IQVIA (Germany) and CPRD GOLD (UK)
Main measure of effect:	Proportion of patients with one of the defined indications of use at time of antibiotic prescribing/dispensing Duration of antibiotic use (expressed as minimum, p25, median, p75, and maximum)

9. RESEARCH METHODS

9.1 Study Type and Study Design

A retrospective cohort study was conducted using routinely-collected health data from 6 databases. The study comprised of two consecutive parts:

1. A population-based cohort study was conducted to address objective 1, assessing the prevalence and incidence of the respective antibiotics of interest (by individual antibiotic and by antibiotic class).
2. A new drug user cohort was used to address objective 2; to characterise patient-level antibiotic utilisation in terms of indication of use and duration of use.

Table 9.1: Description of Potential Study Types and Related Study Designs.

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population Level DUS	Population Level Cohort	Off the shelf (C1)
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)

9.2 Study Setting and Data Sources

This study was conducted using routinely collected data from 6 databases in 5 European countries (4 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Bordeaux University Hospital (CHUBX), France
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Parc Salut Mar Barcelona, Hospital del Mar (IMASIS) (hospital database), Spain
5. IQVIA Disease Analyzer Germany (IQVIA Germany), Germany
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Detailed information on data source is described in **Table 9.2**.

Table 9.2: Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g., primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of subjects	Data lock for the last update
NL	IPCI	Covers primary care setting where antibiotic prescriptions are used	Primary care	EHR	2.7 million	30/6/2022
FR	CHUBX	Covers secondary care setting where antibiotic prescriptions/dispensing are used	Secondary care (in and outpatients)	EHR	2.2 million	18/12/2022
ES	SIDIAP	Covers primary care setting where antibiotic prescriptions are used	Primary care	EHR	8.3 million	31/3/2022
ES	IMASIS	Covers secondary care setting where antibiotic prescriptions are used	Secondary care (in and outpatients)	EHR	1.0 million	9/7/2022
DE	IQVIA Germany	Database covers primary care setting where antibiotic prescriptions are issued.	Primary care and outpatient specialist care	EHR	8.5 million	30/6/2022
UK	CPRD GOLD	Database covers primary care setting where antibiotic prescriptions are issued.	Primary care	EHR	15.7 million	30/6/2020

NL = The Netherlands, FR= France, ES = Spain, DE = Germany, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; CHUBX= Bordeaux University Hospital, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS= Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data

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Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.(8, 9) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996(8). The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board(8).

Bordeaux University Hospital (CHUBX), 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).(10)

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT) managed by the Catalan Health Institute (CHI), consisting of GPs, nurses and other cinical and non-clinical staff(11). The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health InstituteCHI primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Institut Municipal Assistencia Sanitaria 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, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 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. (12)

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings(13). Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD(14) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process.

9.3 Study Period

The study period started on 1st January 2012 until 31st December 2021.

9.4 Follow-up

9.4.1 Population-level Utilization of antibiotics from the WHO Watch list

Subjects in the denominator population began contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2012), 2) date at which they had a year of prior history recorded (except for children <=1 years during the study period). Participants stopped contributing person time at the earliest date of the following: 1) study end date (31st December 2021) or 2) end of available data in each of the data sources or 3) date at which the observation period of the specific person ended.

An example of entry and exit into the denominator population is shown in **Figure 9.1**. 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.

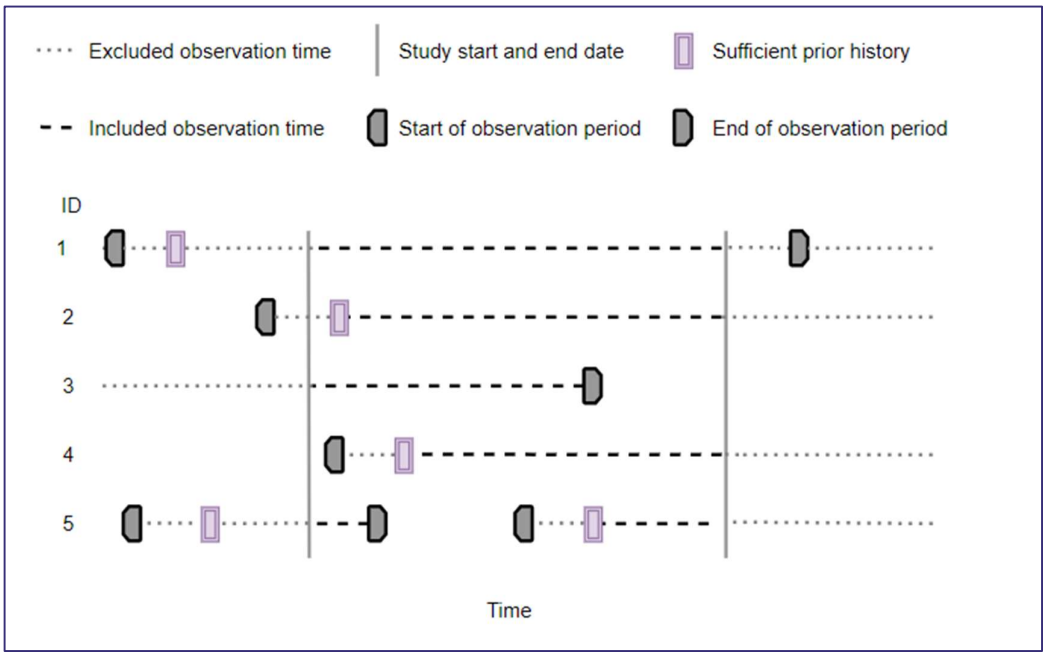


Figure 9.1: Included observation time for the denominator population.

9.5 Study Population with inclusion and exclusion criteria

9.5.1 Population-level Utilisation of the antibiotics of interest

The study cohort comprised of all individual present in the period 2012-2021 (or the latest available), with at least 365 days of data availability before the day they became eligible for study inclusion except for children < 1 year during the study period where this requirement did not hold.

Additional eligibility criteria were applied for the calculation of incidence rates: The observation time of users of the antibiotic of interest was excluded during use and 30 days afterwards.

9.5.2 Patient-level Utilisation of antibiotics

All new users of antibiotics, after 30 days of no use of the specific antibiotic, in the period between 01/01/2012 and 31/12/2021 (or latest date available), with at least 365 days of visibility (except for children <1 year during the study period) prior to the date of their first antibiotic prescription. Start date of new use was used as index date.

Table 9.3: Operational Definitions of Inclusion Criteria.

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2012-2021 (or the latest available)	See under inclusion criterion	After	N/A	Primary care and combination of primary and secondary care for IQVIA Germany and secondary care CHUBX and IMASIS	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	Primary care and combination of primary and secondary care for IQVIA Germany and secondary care CHUBX and IMASIS	N/A	N/A	All individuals within the selected databases	N/A	N/A

* After as first possible study entry date was selected and then it was checked whether patient had one year of database history (except for children).

9.6 Variables

9.6.1. Exposure/s

For this study, the exposure of interest was use (during study period) of antibiotics from the "Watch" category of The WHO 2021 AWaRe classification (who.int) of antibiotics. This Watch category represents antibiotics that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance.

The calculation of duration of the exposures is described under 9.9.2 - drug exposure calculations.

This list of antibiotics (with respective ATC code) can be found in appendix I of the report.

9.6.2. Outcome/s

N/A

9.6.3. Other covariates, including confounders, effect modifiers and other variables

9.6.3.1 Covariates for stratification in population-level drug utilisation study:

- Age: 10-year age bands were used except for the youngest and oldest categories: 0-1, 2-11, 12-17, 18-29, 30-39, 40-49, etc. 80+
- Calendar year
- Sex

9.6.3.2 Covariates for patient-level drug utilisation study:

- The following conditions of interest (i.e., indication of use) based on infectious disease categories as applied by ECDC in their point prevalence studies on use of antibiotics(15):
    - Bloodstream Infection
    - Bone and Joint Infection
    - Cardiovascular System Infection
    - Catheter-related Infection
    - Central Nervous System Infection
    - Eye, Ear, Nose, Throat or Mouth Infection
    - Gastrointestinal System Infection
    - Genito-Urinary Tract Infection
    - Lower Respiratory Tract Infection other than pneumonia
    - Pneumonia
    - Reproductive Tract Infection
    - Skin and Soft Tissue Infection
    - Surgical Site Infection
    - Other Infection
- Top 10 of co-morbidities from large-scale patient characterisation

The operational definitions of exposure and covariates are described in table 9.4 and table 9.5 below.

Table 9.4: Exposure details.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to…	Measurement characteristics / validation	Source of algorithm
Antibiotics from the "Watch" category of The WHO 2021 AWaRe classification	Preliminary code lists provided in Appendix 1	[-30, -1]	Calendar year	Primary and secondary care	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

Table 9.5: Operational definition of Covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Indication of Use	Check for conditions of interest related to use of antibiotics	Counts	At index date and as sensitivity analyses in windows around index date: [-7, 7] and [-30, 7]	Primary and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A
Comorbidity	Large-scale patient-level characterisation with regard to underlying comorbidity	Counts	At index date (ID), for 30 to 1 day before ID,	Primary care and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A
Route of administration	Oral or parenteral	Count	At index date	Primary and secondary care	RxNorm	N/A	All new users	N/A	N/A

9.7 Study size

No sample size has been calculated. Feasibility counts had been generated for this drug utilisation study in the general population of the respective databases.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. After all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results.

The study results of all data sources were checked after which they were made available to the team and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.2 Complete Catalogue of Standard Analyses which describes the type of analysis in function of the study type.

Table 9.6: Description of Study Types and Type of analysis.

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population Level DUS	Off-the-shelf (C1)	- Population-based incidence rates - Population-based prevalence
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features for new antibiotic users - Frequency and % of indication/s - Estimation of minimum, p25, median, mean, p75, and maximum treatment duration

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were clouded.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilisation" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package for the population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras were defined as follows: Exposure started at the date of the first prescription. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM.

Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug prescriptions were merged into one continuous drug era if the distance in days between end of the first prescription and start of the second prescription was ≤ 7 days. The time between the two joined prescriptions was considered as exposed as shown in the first row in **Figure 9.2**. Note: dose is not considered for this study.

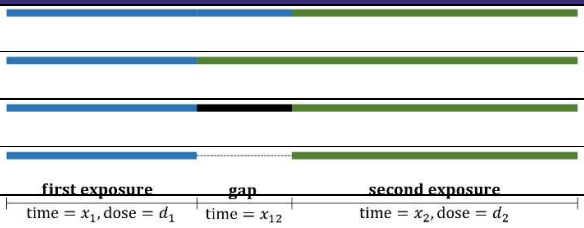
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 9.2: Gap era joint mode.

If two prescriptions overlapped, the overlap time was considered exposed by the first prescription (**Figure 9.3**). No time was added at the end of the combined drug era to account for the overlap.

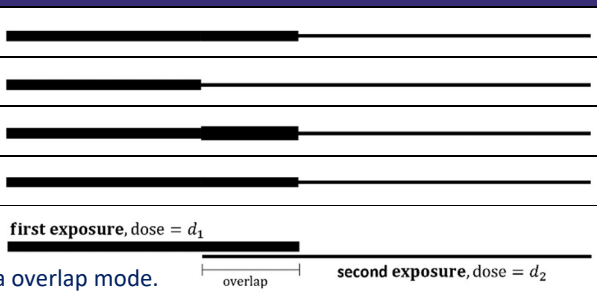
Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 9.3: Gap era overlap mode.

If two prescriptions started at the same date, the overlapping period was considered exposed by both. We did not consider repetitive exposure.

New user cohorts

New users were selected based on their prescriptions of the respective drug of interest after the start of the study. For each patient, at least 365 days of data visibility was required prior to a prescription. New users were required to not have been exposed to the drug of interest for at least 30 days prior to the current prescription. If the start date of a prescription did not fulfil the exposure washout criteria of 30 days of no use, the whole exposure was eliminated.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: 0-1, 2-11, 12-17, 18-29, 30-39, 40-49, etc. 80+

Sex

Results were presented stratified by sex for antibiotic class level (not for the individual antibiotic of interest)

Indication

Indication was determined based on recordings of pre-defined conditions (see 9.6.3.2 – other variables), at the date of the first prescription of the respective drug (index date)[primary definition] or during assessment windows [sensitivity analyses]. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other condition, the person was considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation was conducted. Co-variates were extracted for the following time intervals: Concepts in the "condition" domain were assessed for 30 to 1 day before index date, and at index date. The top-10 for both time windows are presented.

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

Population-level drug utilisation study

Prevalence and incidence calculations were conducted separately for each antibiotic of interest as well as by antibiotic class.

Prevalence calculations

Prevalence will be calculated as annual period prevalence which summarises the total number of individuals who use the drug of interest during a given year divided by the population at risk of getting exposed during that year. Therefore, period prevalence gives the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals will be calculated.

An illustration of the calculation of period prevalence is shown below in **Figure 9.4**. Between time t+2 and t+3, two of the five study participants are antibiotic users giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants being an antibiotic user, giving a prevalence of 20%.

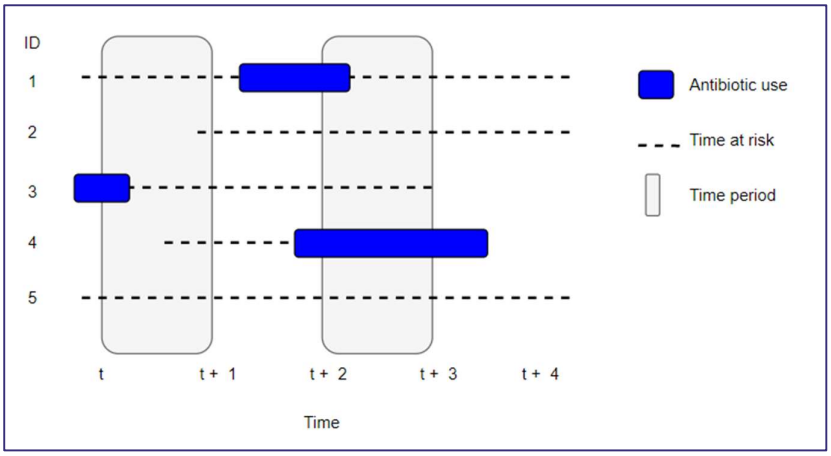


Figure 9.4: Period prevalence example for antibiotic use.

Incidence calculations

Annual incidence rates of the antibiotics of interest were calculated as the 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. 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) were excluded. Those study participants who enter the denominator population contributed time at risk up to their first prescription during the study period. If they did not have a drug exposure, they contributed time at risk up as described above in section 9.3 and 9.4 (study period and end of follow-up). Incidence rates were given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of antibiotic use is shown below in **Figure 9.5**. 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.

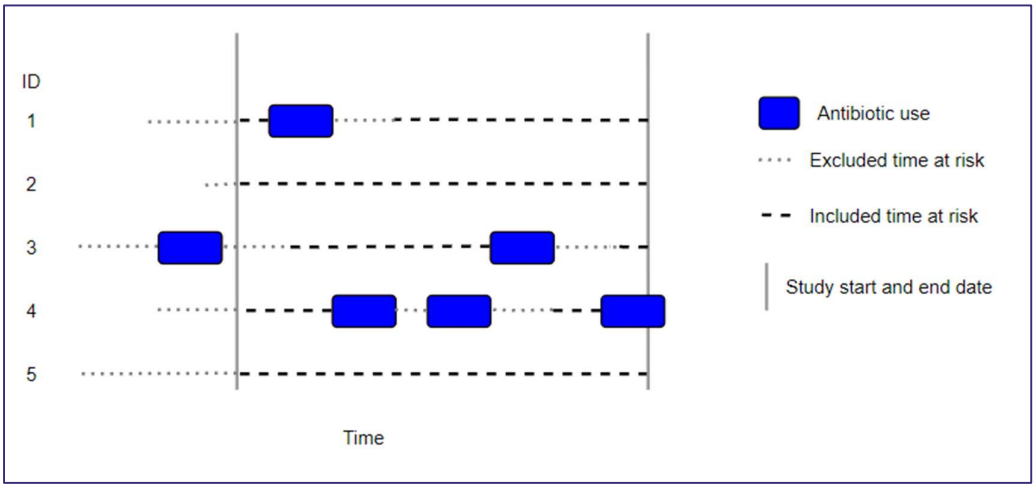


Figure 9.: Incidence example for antibiotic use.

Patient-level drug utilisation study

New drug user patient-level 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 was provided.

Indication

The number of persons (N, %) with a record of the respective indication was provided. If a person had a record of more than one specific indication, that person was included in both specific indication groups separately.

Treatment duration

Treatment duration was calculated as the duration of the first continuous exposure episode. Estimations of treatment duration were summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases, where duration could not be calculated due to e.g. missing information on quantity or dosing, treatment duration was not provided.

9.9.5 Methods to control for potential sources of bias

NA

9.9.6 Methods to deal with missing data

For the drug utilisation studies we assumed that the absence of a prescription records meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that that condition was not the indication for the drug prescription.

9.9.7 Description of sensitivity analyses

Indication of use was explored in a period of 7 days +/- the index date and in a period from 30 days before until 7 days after index date

9.9.8 Evidence synthesis

Results from analyses described are presented separately for each database and no pooling of results was conducted.

9.10 Deviations from the protocol

Included databases and analyses:

Population level and Patient-level drug utilisation analyses were provided for all databases. As in CHUBX, drugs were mapped to the ingredient level and not to the clinical drug level, stratified analysis by route of administration could not provided for this database.

Statistical analyses:

For treatment duration in addition to median, mean was provided with standard deviation.

Stratified analysis:

Because of the large number of individual antibiotics, age and sex stratification was done for the antibiotic subclasses but not for the individual antibiotic drugs.

Because of the volume of data, 10 year age bands were used to define age categories and not 5-year age bands as described in the original protocol.

10. DATA MANAGEMENT

10.1. Data management

All databases have been mapped to the OMOP common data model. This enabled the use of standardised analytics and 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.

This analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for this study report.

10.2. Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which were 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 were 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 were run, which generated non-identifiable

aggregate summary results. All and any results with n<5 participants were obscured using cell suppression to minimise risk of reidentification.

11. 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). In particular, it was expected that data partners would have run the OHDSI Data Quality **Dashboard** tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focused 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 was 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 had one or more subcategories and were evaluated in two contexts: validation and verification. Validation related to how well data aligned with external benchmarks with expectations derived from known true standards, while verification related to how well data conformed to local knowledge, metadata descriptions, and system assumptions. Additionally, two more tools were used to control the quality of data during the onboarding. **Achilles** for database characterisation, running 293 analyses against the data. This output is not shared with the DARWIN-EU® CC as it reveals granular information of the data. It is expected that the data partners review the Achilles output internally. Secondly, **CdmOnboarding** generates a Word report with the most important database characteristics, providing insight in the readiness of the database to use for network studies. The output is shared with and inspected by the DARWIN-EU® CC.

Study specific quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. An MD reviewed the codes for all the antibiotics from the WHO Watch list.

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

12. RESULTS

All results are available in a web-application (“shiny app”) at. https://data-dev.darwin-eu.org/EUPAS103381/.

12.1. Population-level DUS

12.1.1. Participants

Table 12.1.1 describes the number of people included and excluded by each criterion. The total number of individuals available for analysis consisted of 33,929,787 of which 8,215,316 (24.2%) from CPRD GOLD, 2,283,830 (6.7%) from IPCI, 14,854,799 (43.8%) from IQVIA Germany, 7,310,575 (21.5%) from SIDIAP, 339,946 (1.0%) from IMASIS and 925,321 (2.7%) from CHUBX. In all databases, individuals mainly were

excluded from the analysis for reasons of not having observation time during study period, not having sufficient database history or not having sufficient follow-up time to calculate incidence and prevalence.

Table 12.1.1: Number of participants in each source population during the study period overall.

		CPRD GOLD		IPCI		IQVIA Germany		SIDIAP		IMASIS		CHUBX	
step	**reason**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**
General	Starting population	15,662,217		2,674,547		40,243,608		8,265,343		1,014,735		2,152,385	
General	Missing year of birth	15,662,217	0	2,674,547	0	40,243,608	0	8,265,343	0	1,014,735	0	2,152,385	0
General	Missing sex	15,662,217	0	2,674,547	0	40,215,065	28,543	8,265,343	0	1,014,735	0	2,151,830	555
General	Cannot satisfy age criteria during the study period based on year of birth	15,662,217	0	2,674,547	0	40,215,065	0	8,265,343	0	1,014,735	0	2,151,828	2
General	No observation time available during study period	9,100,738	6,561,479	2,572,584	101,963	32,451,337	7,763,728	7,575,821	689,522	595,332	419,403	1,930,191	221,637
General	Doesn't satisfy age criteria during the study period	9,100,738	0	2,572,584	0	32,451,337	0	7,575,821	0	595,332	0	1,930,191	0
General	Prior history requirement not fulfilled during study period	8,215,316	885,422	2,283,830	288,754	14,854,799	17,596,538	7,310,575	265,246	339,946	255,386	925,321	1,004,870
General	No observation time available after applying age and prior history criteria	8,215,316	0	2,283,830	0	14,854,799	0	7,310,575	0	339,946	0	925,321	0
Prevalence	Starting analysis population	8,215,316		2,283,830		14,854,799	0	7,310,575		339,946		925,321	
Prevalence	Not observed during the complete database interval	8,142,325	72,991	2,213,458	70,372	14,854,799	0	7,247,009	63,566	337,802	2,144	907,805	17,516
Incidence	Starting analysis population	8,215,316		2,283,830		14,854,799		7,310,575		339,946		925,321	
Incidence	Excluded due to prior event (do not pass outcome washout during study period)	8,215,311	5	2,283,828	2	14,853,756	1043	7,310,559	16	339,946	0	925,319	2
Incidence	Not observed during the complete database interval	8,215,311	0	2,283,828	0	14,853,756	0	7,310,559	0	339,946	0	907,803	17,516

12.1.2. Descriptive Data

For this study, no patient characteristics on individuals being prescribed/dispensed antibiotics is collected except for age, sex, indication of use and top 10 of disease codes at time of antibiotic prescribing. Information on age and sex is included as part of the population level estimates on the incidence and prevalence of antibiotic use. The indication of use and top 10 of comorbidities is presented in the patient level DUS results.

12.1.3. Outcome Data

For this study, no specific outcomes of interest are studied.

12.1.4. Main Results

Incidence rates of the antibiotics of the WHO Watch list

The Watch list from the WHO consists of 141 antibiotics (137 individual antibiotics with some additional entries for oral or parenteral use). Of these 137 antibiotics, 133 were mapped to the OMOP CDM (i.e. existence of ingredient level code). Of these 133 antibiotics, only 78 were actually prescribed in at least one of the data sources during the study period.

The table with overall incidence rates of the different antibiotics of the WHO Watch list is available as appendix to the report (Table 1 – overall incidence of antibiotic use).

And although 78 antibiotics were prescribed during the study period, only for a limited number of antibiotics, incidence rates were above 100/100,000 PY.

Because of the large number of individual antibiotics, not each antibiotic can be discussed in detail. Table 12.4.1-1 describes the top 20 of highest incidence rates per database.

Although incidence rates varied slightly between the different primary care databases (CPRD GOLD, IPCI and SIDIAP), results on those antibiotics with the highest incidence rates were comparable with ciprofloxacin being in the top 3 (984/100,000 PY in IQVIA Germany,1,023/100,000 PY in CPRD GOLD, 1,462/100,000 PY in IPCI and 2,098/100,000 PY in SIDIAP). Other antibiotics from the Watch list, frequently prescribed in primary care were clarithromycin (CPRD GOLD and IPCI), fosfomycin (IPCI, IQVIA Germany and SIDIAP) and azithromycin (IPCI, IQVIA Germany and SIDIAP). In IQVIA Germany, also use of second generation cephalosporins belonged to the top 5 with an incidence rate of 1,352/100,000 PY for cefuroxime and 536/100,000 PY for cefaclor. Results from IMASIS and CHUBX represent antibiotic prescribing in secondary care. In IMASIS, use of levofloxacin and ciprofloxacin were the highest with an incidence rate of 1,218/100,000 PY for levofloxacin and 1,213/100,000 PY for ciprofloxacin. Antibiotic prescribing was lower in CHUBX with the highest use for ceftriaxone (961/100,000 PY). The prescribing patterns were different in secondary care compared to primary care with a higher use of ceftriaxone, vancomycin, piperacillin+tazobactam and meropenem.

The incidence rates by database and calendar year of those antibiotics most frequently prescribed (top 5) amongst the databases are presented in figure 12.1.4-1 to 12.1.4-15. Figures representing incidence rates by database over time of all different antibiotics are available in the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/)

Table 12.1.4-1: Incidence rate (per 100,00 PY, with 95% confidence intervals) of antibiotics from the WHO Watch list – top 20.

CPRD GOLD		IPCI		SIDIAP		IMASIS		CHUBX		IQVIA Germany	
Incidence	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**
3,577 (3,571; 3,583)	Clarithromycin	1,862 (1,853; 1,870)	Azithromycin	3,165 (3,160; 3,169)	Fosfomycin	1,218 (1,202; 1,234)	Levofloxacin	961 (952; 970)	Ceftriaxone	1353 (1350; 1355)	Cefuroxime
2,073 (2,068; 2,078)	Erythromycin	1,462 (1,455; 1,470)	Ciprofloxacin	2,567 (2,563; 2,571)	Azithromycin	1,213 (1,197; 1,229)	Ciprofloxacin	493 (487; 499)	Piperacillin_ tazobactam	985 (983;987)	Ciprofloxacin
1,023 (1,020; 1,026)	Ciprofloxacin	1,190 (1,184; 1,197)	Fosfomycin	2,098 (2,094; 2,101)	Ciprofloxacin	980 (966; 994)	Ceftriaxone	204 (200; 208)	Ofloxacin	981 (979; 984)	Azithromycin
868 (865; 871)	Lymecycline	828 (822; 834)	Clarithromycin	1,485 (1,482; 1,488)	Levofloxacin	831 (818; 844)	Azithromycin	191 (187; 195)	Ciprofloxacin	587 (585; 589)	Fosfomycin
518 (515; 520)	Oxytetracycline	517 (512; 521)	Pheneticillin	959 (956; 961)	Cefuroxime	830 (817; 843)	Fosfomycin	133 (129; 136)	Vancomycin	537 (535; 539)	Cefaclor
361 (359; 363)	Azithromycin	206 (204; 209)	Minocycline	813 (810; 815)	Clarithromycin	351 (343; 360)	Cefotaxime	131 (128; 134)	Levofloxacin	479 (477; 480)	Clarithromycin
73 (72; 73)	Ofloxacin	156 (153; 158)	Norfloxacin	623 (621; 625)	Norfloxacin	277 (270; 285)	Meropenem	125 (122; 128)	Spiramycin	377 (375; 378)	Roxithromycin
48 (48; 49)	Minocycline	142 (139; 144)	Oxytetracycline	345 (344; 347)	Cefixime	194 (188; 200)	Cefixime	89 (86; 92)	Tobramycin	326 (324; 327)	Levofloxacin
43 (43; 44)	Cefaclor	102 (100; 104)	Erythromycin	188 (187; 189)	Moxifloxacin	170 (164; 176)	Vancomycin	79 (77; 82)	Rifampicin	285 (284; 287)	Cefpodoxime-proxetil
31 (30; 31)	Fosfomycin	79 (78; 81)	Levofloxacin	173 (172; 174)	Rifaximin	161 (155; 167)	Ceftazidime	75 (73; 78)	Azithromycin	252 (251; 254)	Ofloxacin
29 (28; 29)	Levofloxacin	51 (49; 52)	Ofloxacin	97 (97; 98)	Spiramycin	159 (153; 165)	Ertapenem	64 (61; 66)	Erythromycin	199 (198; 200)	Erythromycin
18 (17; 18)	Rifampicin	40 (39; 41)	Moxifloxacin	94 (93; 94)	Erythromycin	144 (138; 149)	Cefuroxime	63 (61; 66)	Ceftazidime	141 (140; 142)	Kanamycin
12 (12; 13)	Cefuroxime	39 (38; 40)	Ceftriaxone	85 (84; 86)	Oxytetracycline	91 (87; 96)	Erythromycin	55 (53; 57)	Pristinamycin	122 (122; 123)	Moxifloxacin
6 (5; 6)	Fusidic-acid	22 (21; 22)	Rifampicin	46 (46; 47)	Rifampicin	90 (86; 95)	Clarithromycin	46 (44; 48)	Meropenem	105 (105; 106)	Cefixime
6 (5; 6)	Norfloxacin	17 (16; 18)	Cefuroxime	42 (42; 43)	Josamycin	80 (76; 84)	Rifampicin	37 (35; 39)	Cefixime	75 (74; 75)	Minocycline
5 (4; 5)	Rifaximin	12 (11; 13)	Roxithromycin	29 (28; 29)	Ceftriaxone	49 (46; 52)	Minocycline	35 (34; 37)	Cefuroxime	74 (73; 74)	Norfloxacin
4 (4; 4)	Moxifloxacin	8 (7; 8)	Cefaclor	23 (22; 23)	Fusidic-acid	45 (42; 48)	Norfloxacin	35 (33; 36)	Cefotaxime	32 (32; 33)	Neomycin
4 (4; 4)	Cefixime	3 (3; 4)	Vancomycin	8 (8; 8)	Tobramycin	41 (38; 44)	Moxifloxacin	25 (23; 26)	Fosfomycin	26 (25; 26)	Ceftibuten
3 (3; 3)	Vancomycin	3 (2; 3)	Ceftibuten	7 (7; 7)	Cefonicid	29 (26; 31)	Cefonicid	25 (23; 26)	Cefoxitin	8 (8; 8)	Rifaximin
2 (2; 2)	Ceftriaxone	2 (2; 2)	Pipemidic-acid	5 (5; 5)	Ceftibuten	14 (12; 15)	Tobramycin	20 (18; 21)	Rifaximin	7 (7; 8)	Rifampicin

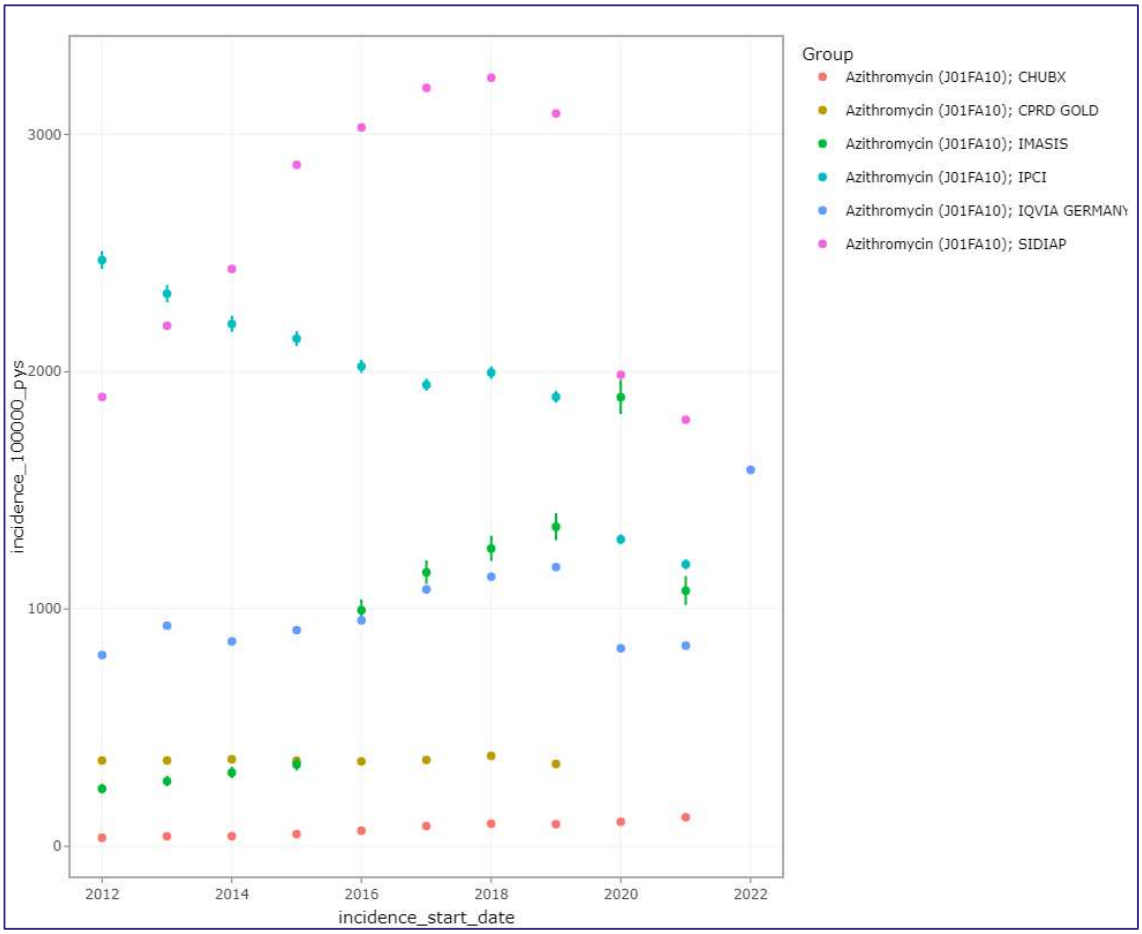


Figure 12.4.1-1: Incidence rates of azithromycin.

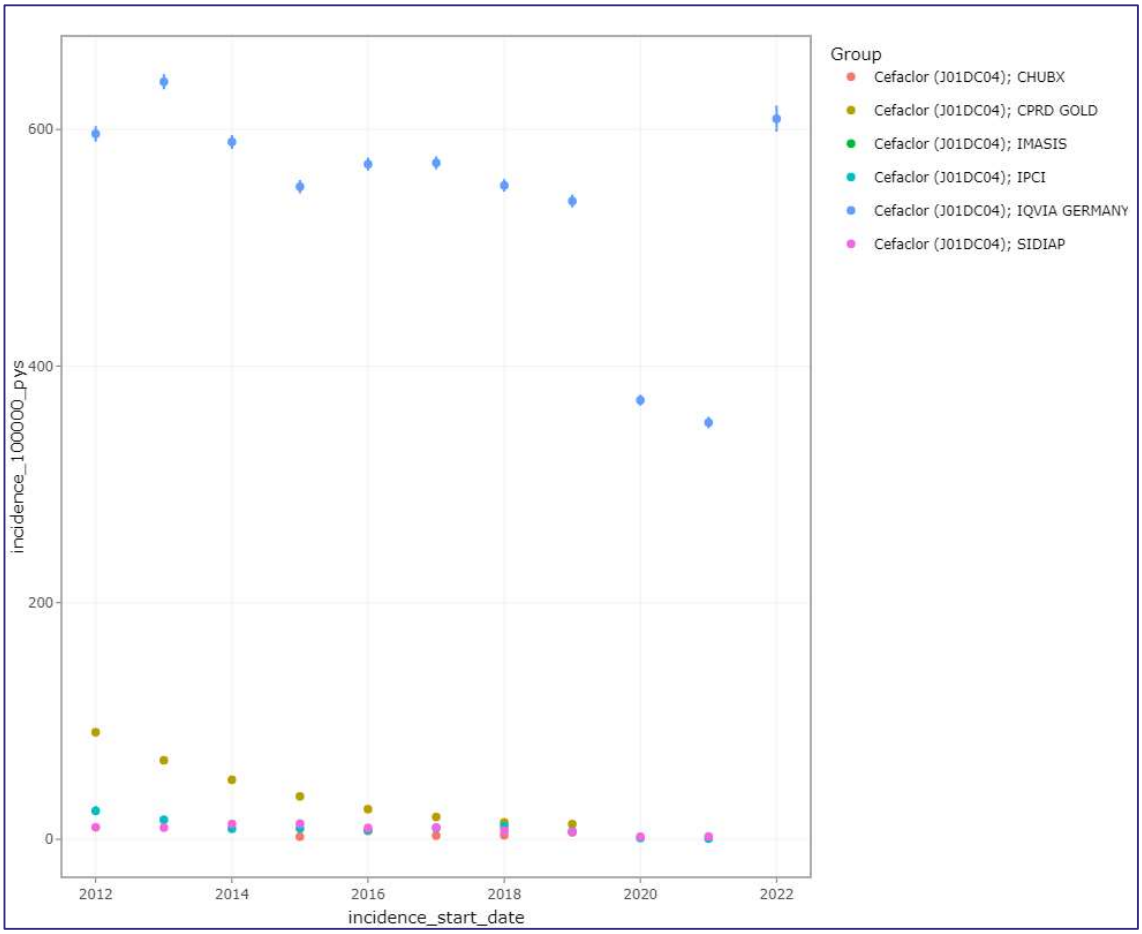


Figure 12.4.1-2: Incidence rates of cefaclor.

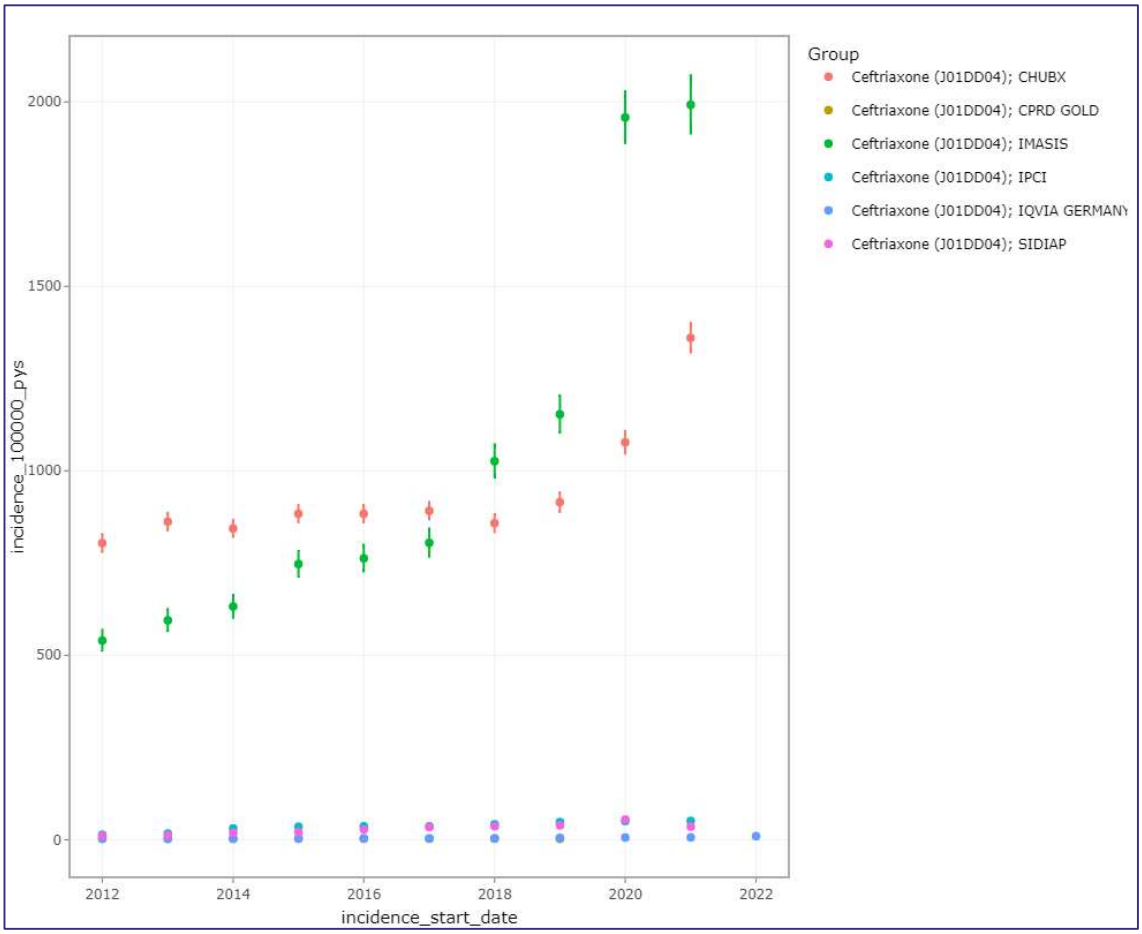


Figure 12.4.1-3: Incidence rates of ceftriaxone.

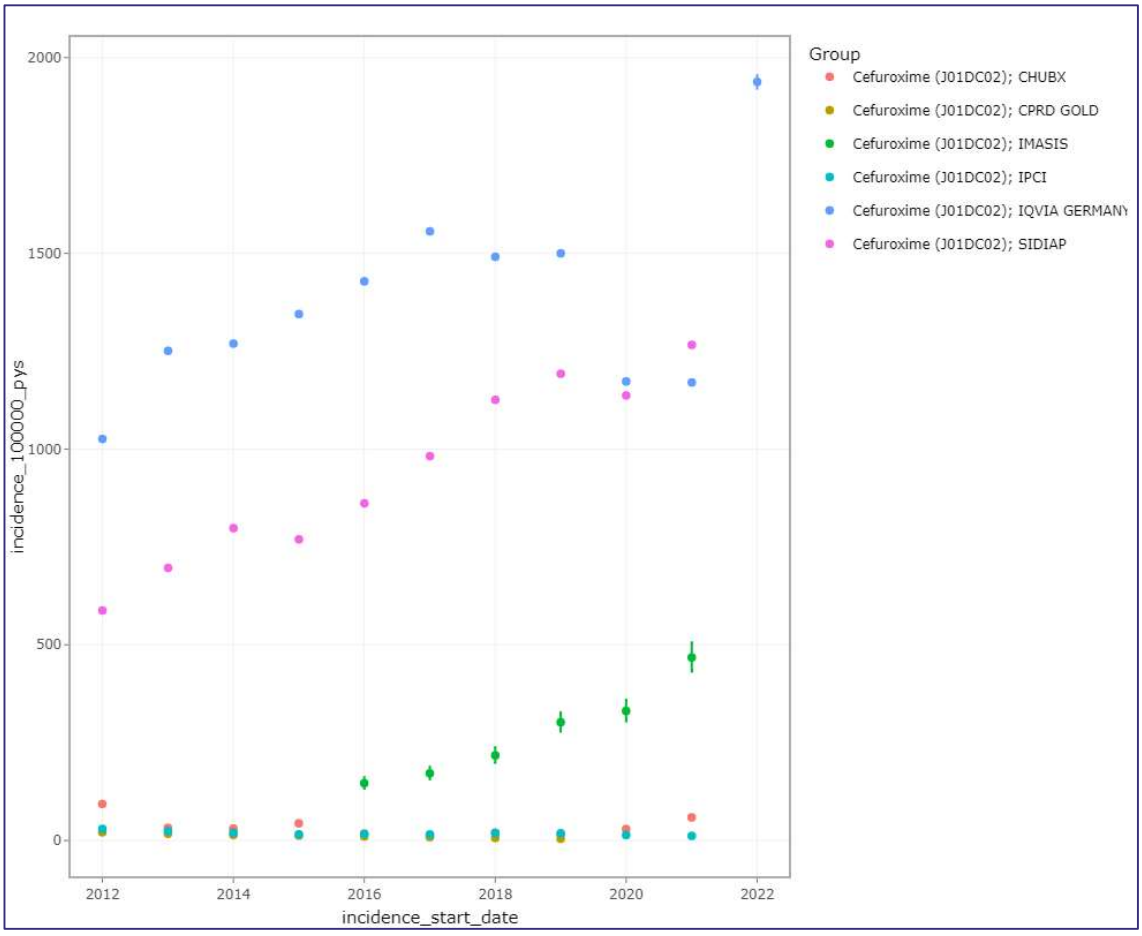


Figure 12.4.1-4: Incidence rates of cefuroxime.

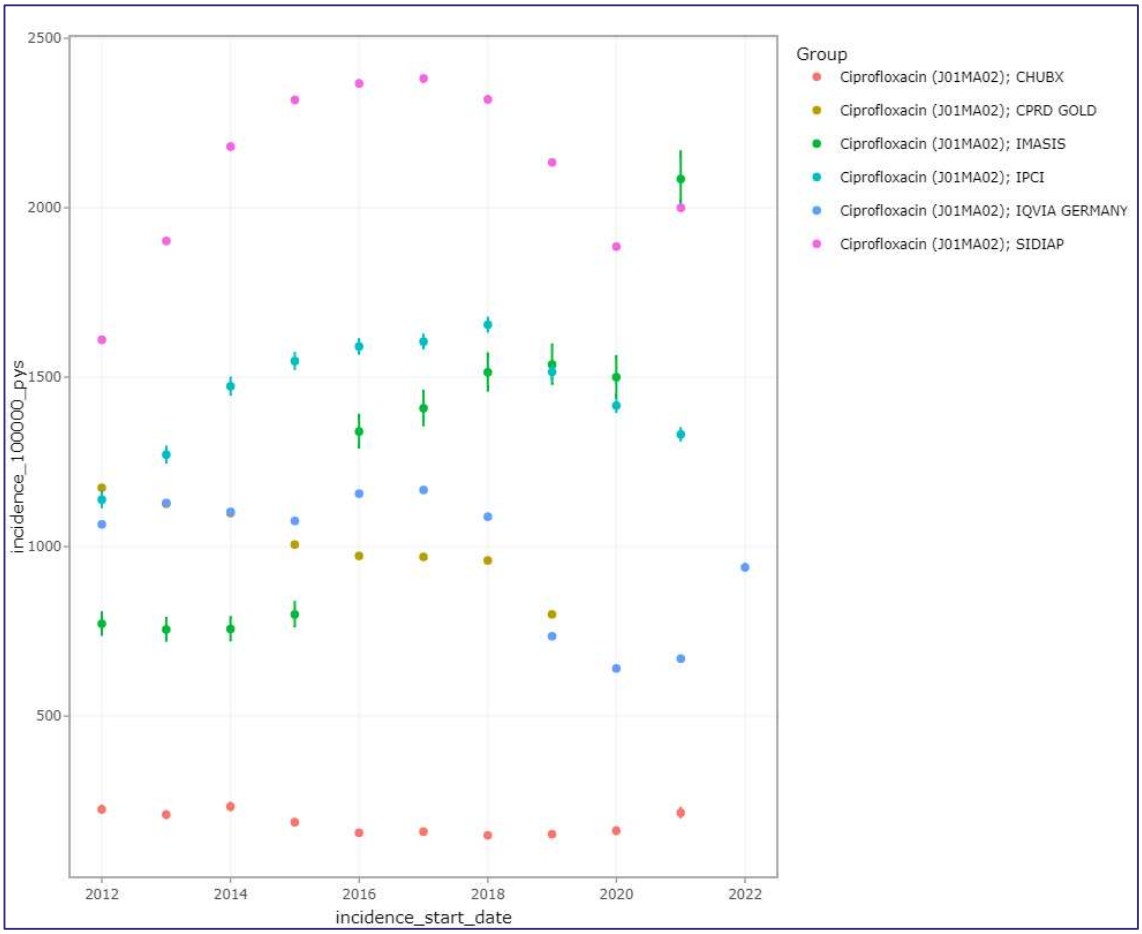


Figure 12.4.1-5: Incidence rates of ciprofloxacin.

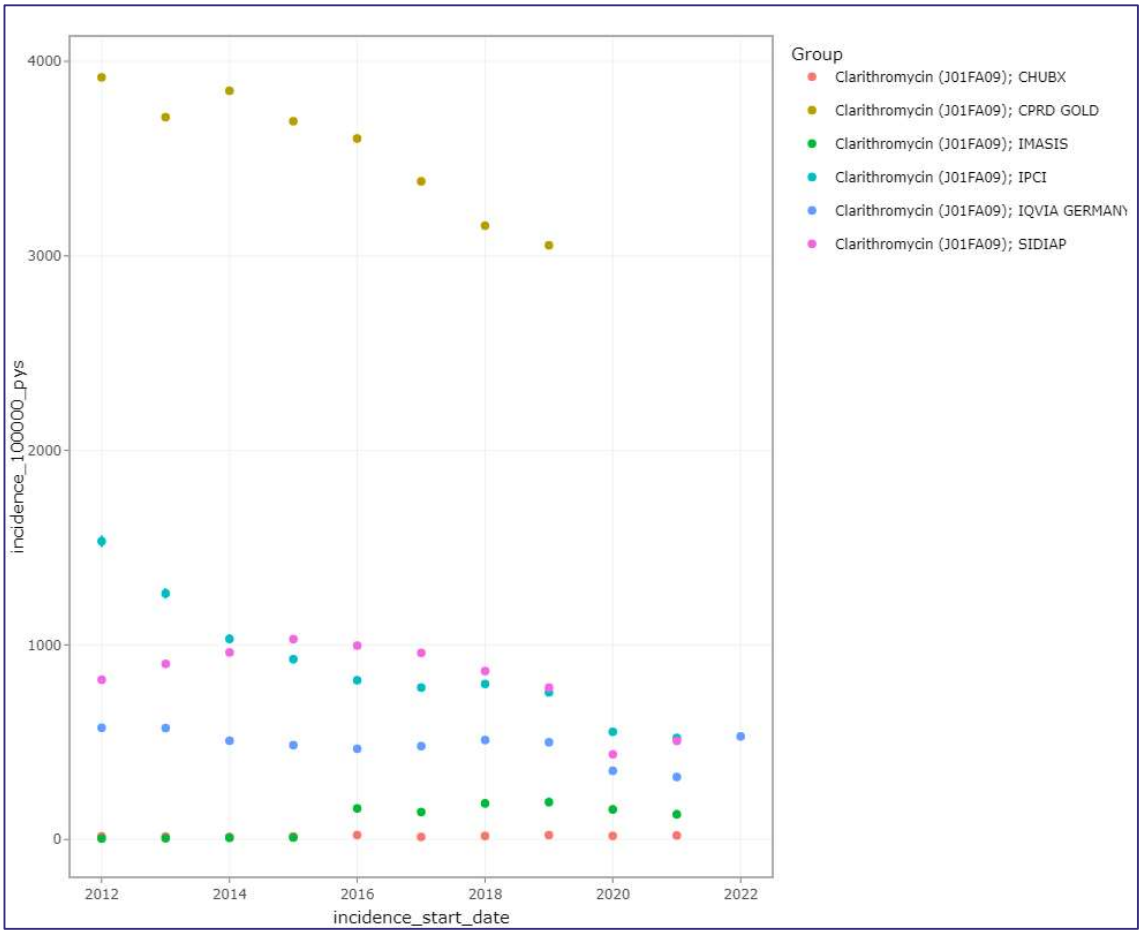


Figure 12.4.1-6: Incidence rates of clarithromycin.

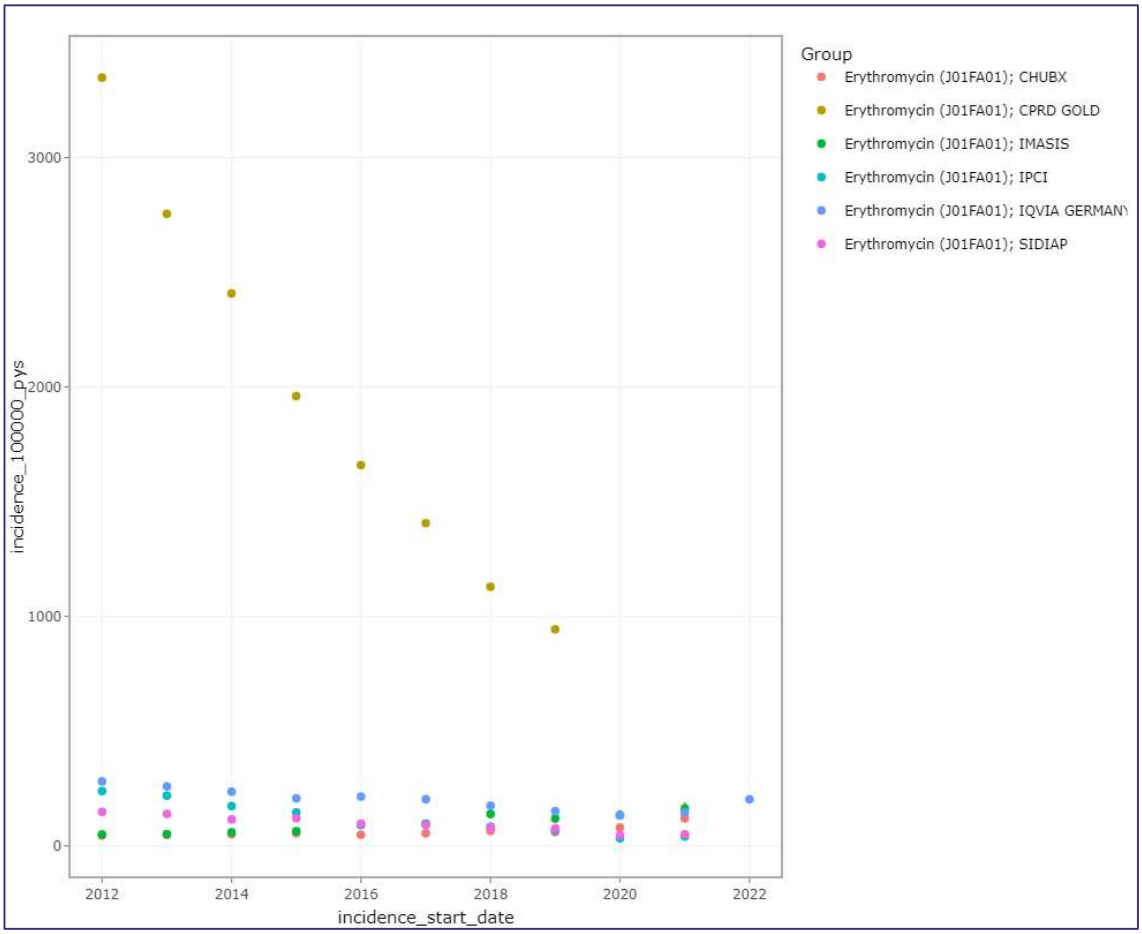


Figure 12.4.1-7: Incidence rates of erythromycin.

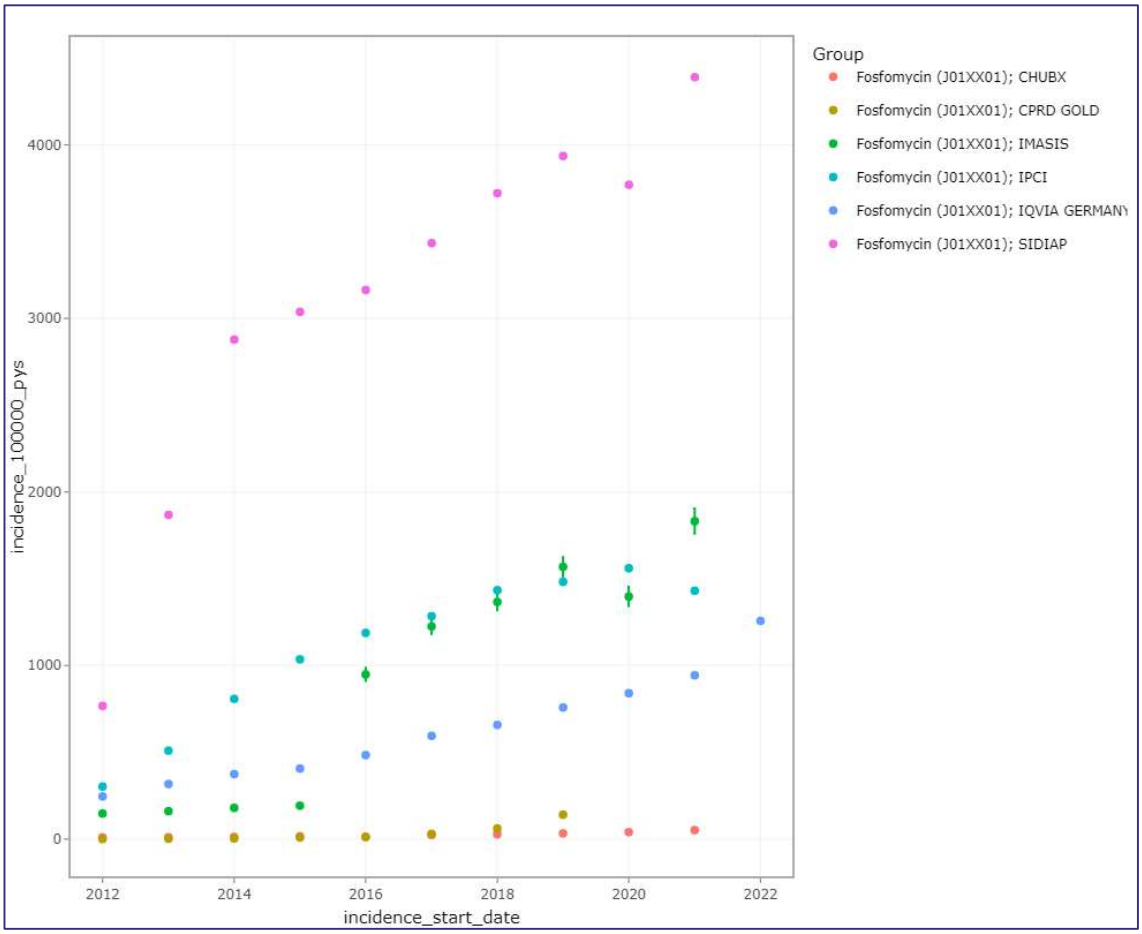


Figure 12.4.1-8: Incidence rates of fosfomycin.

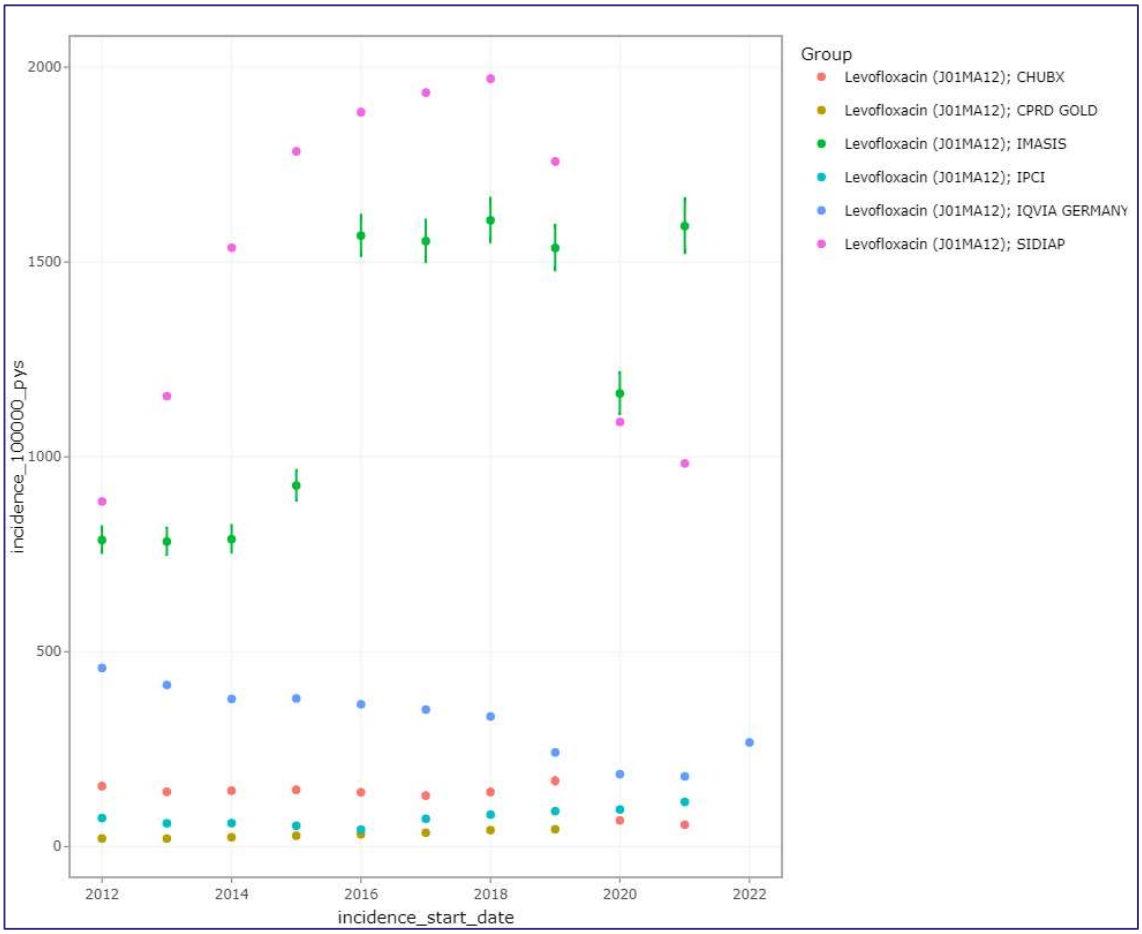


Figure 12.4.1-9: Incidence rates of levofloxacin.

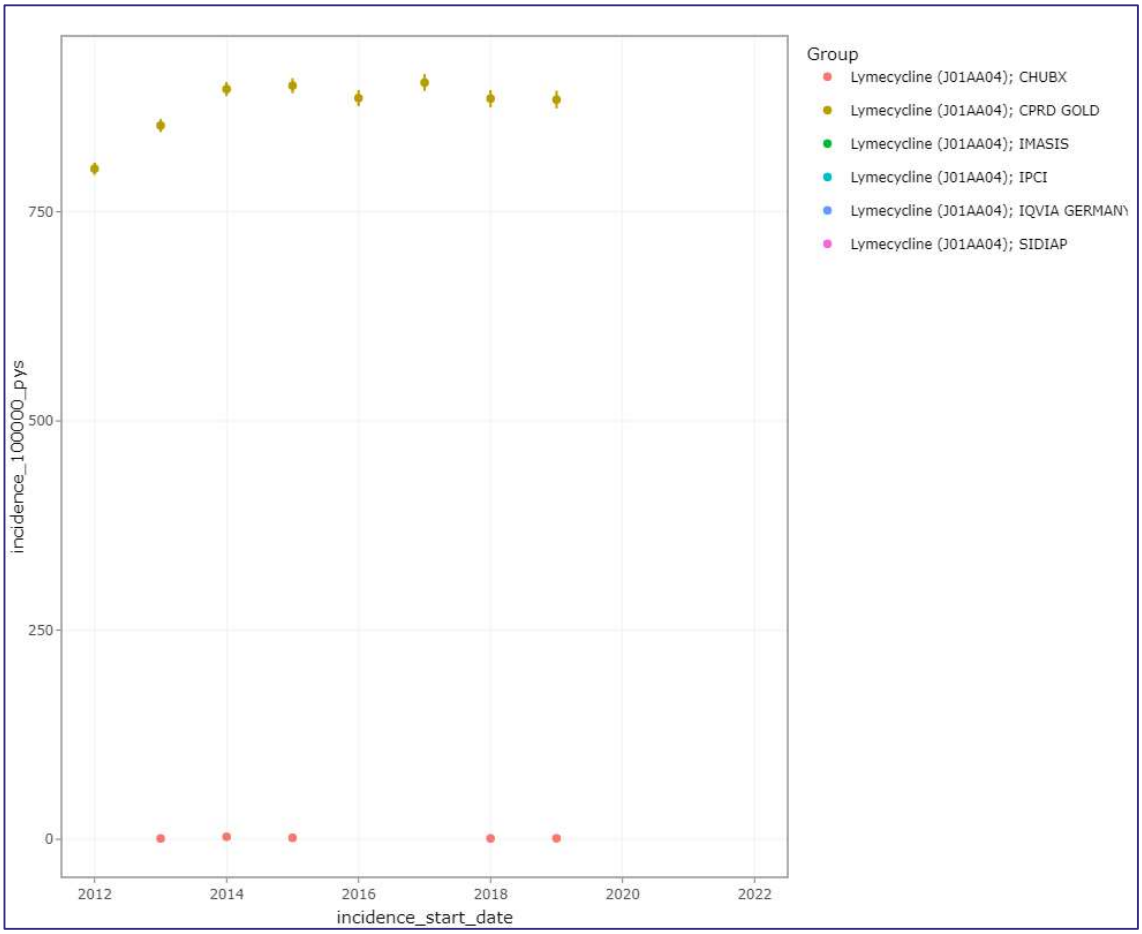


Figure 12.4.1-10: Incidence rates of lymecycline.

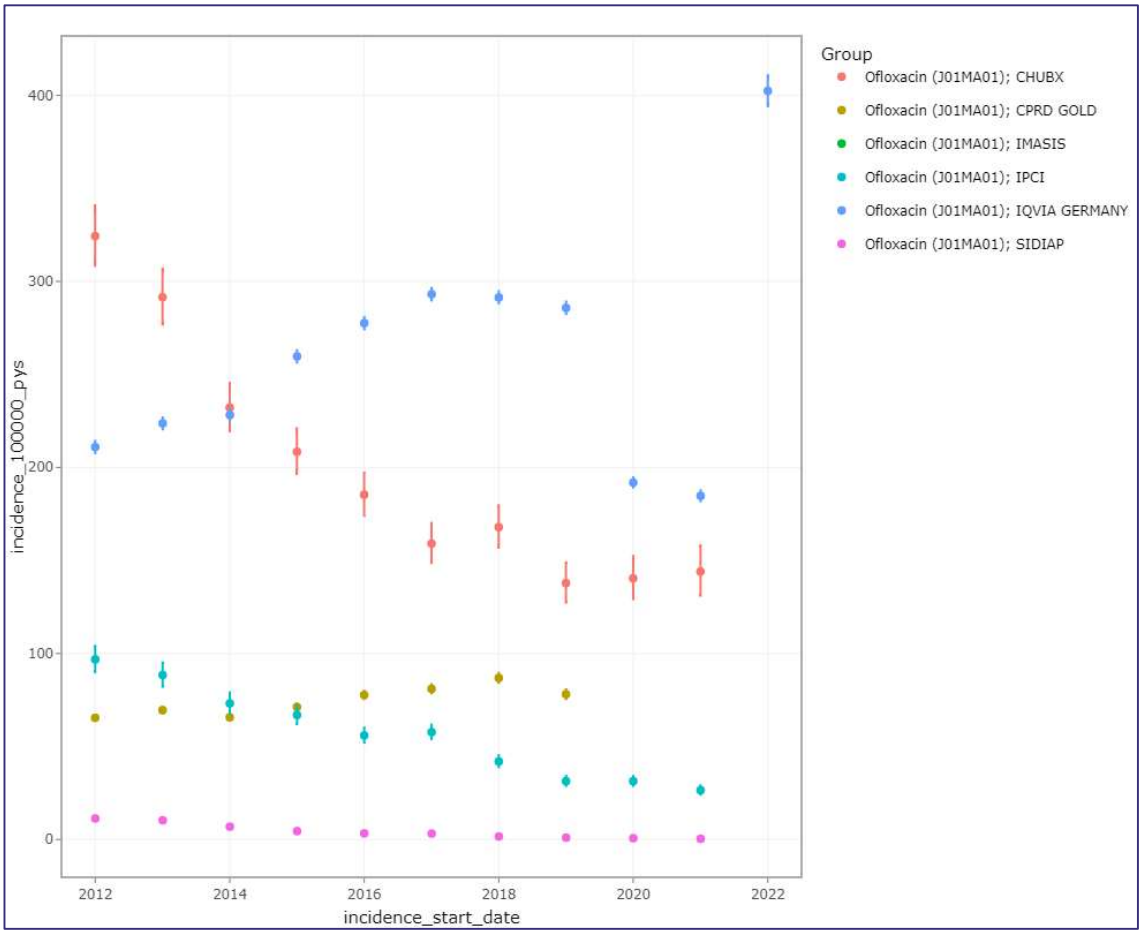


Figure 12.4.1-11: Incidence rates of ofloxacin.

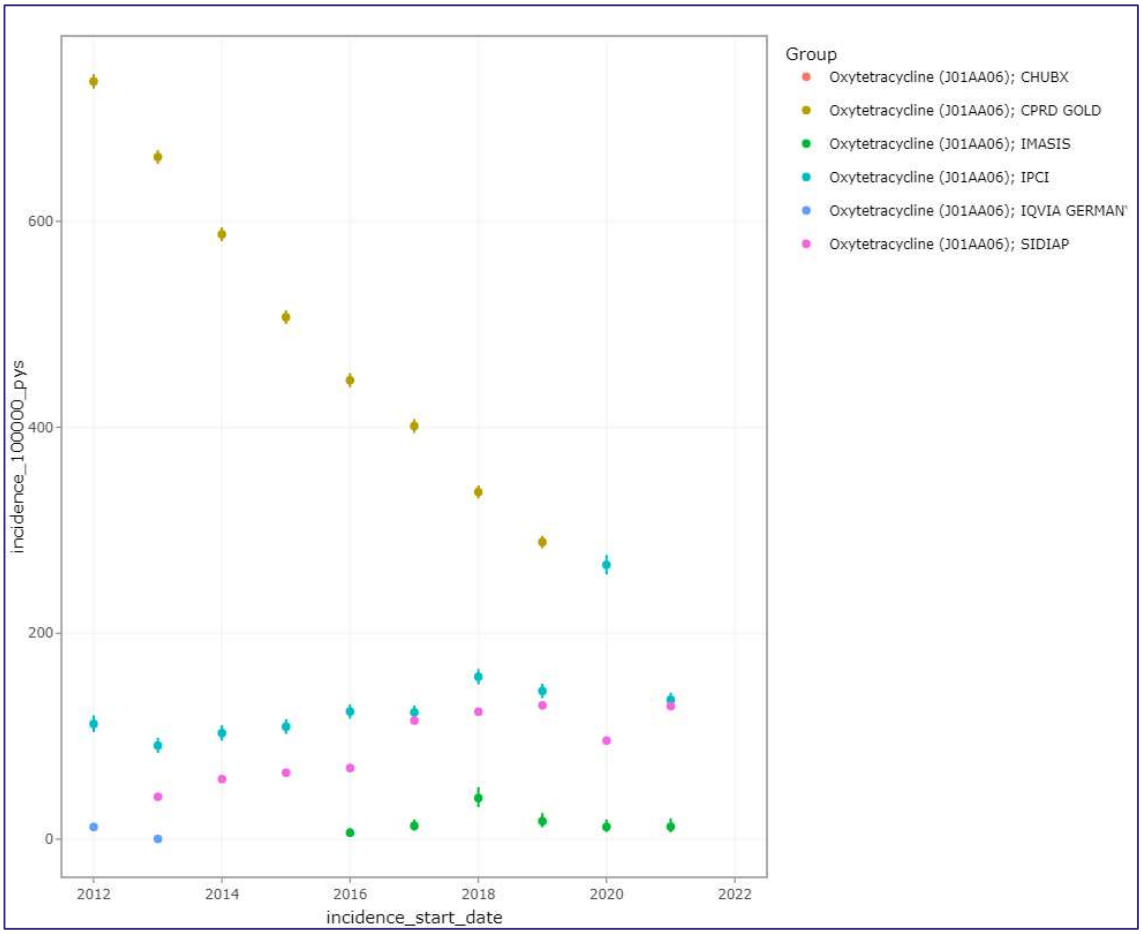


Figure 12.4.1-12: Incidence rates of oxytetracycline.

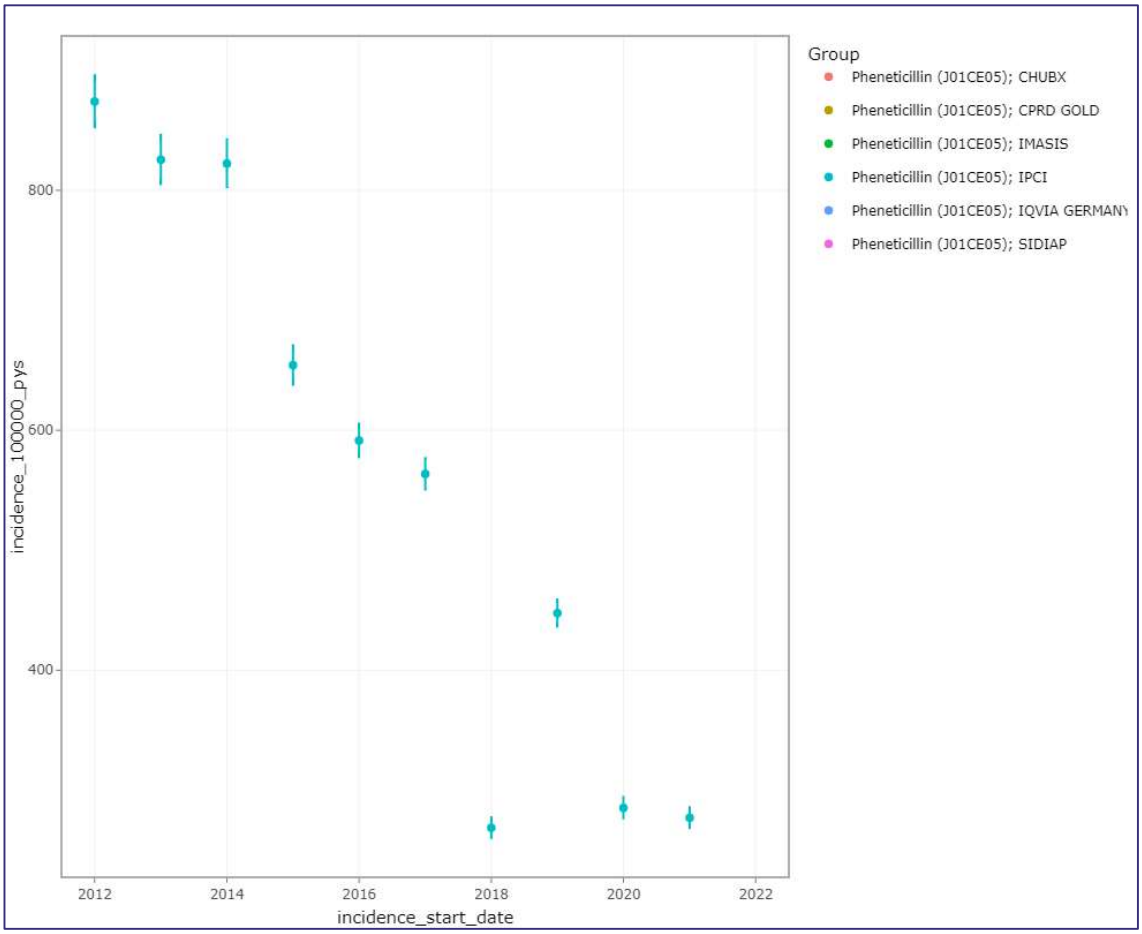


Figure 12.4.1-13: Incidence rates of pheneticillin.

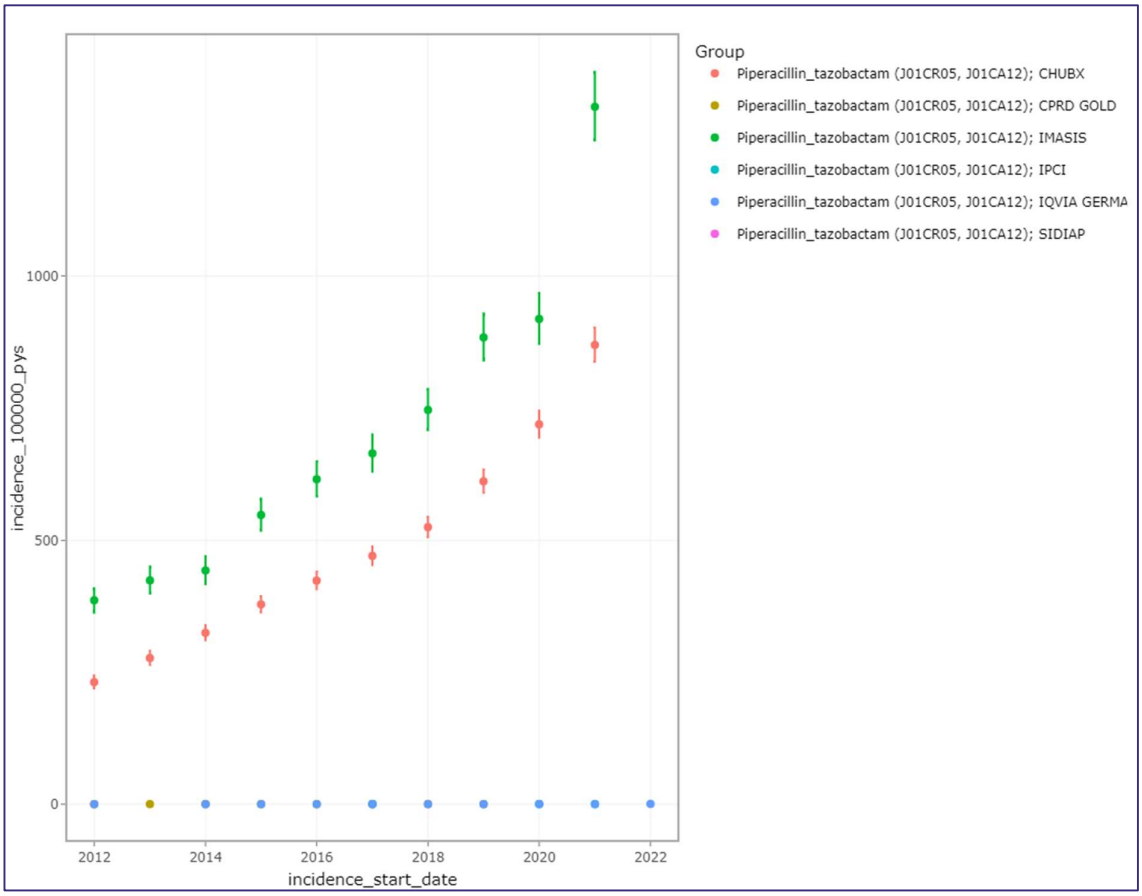


Figure 12.4.1-14: Incidence rates of piperacillin_tazobactam.

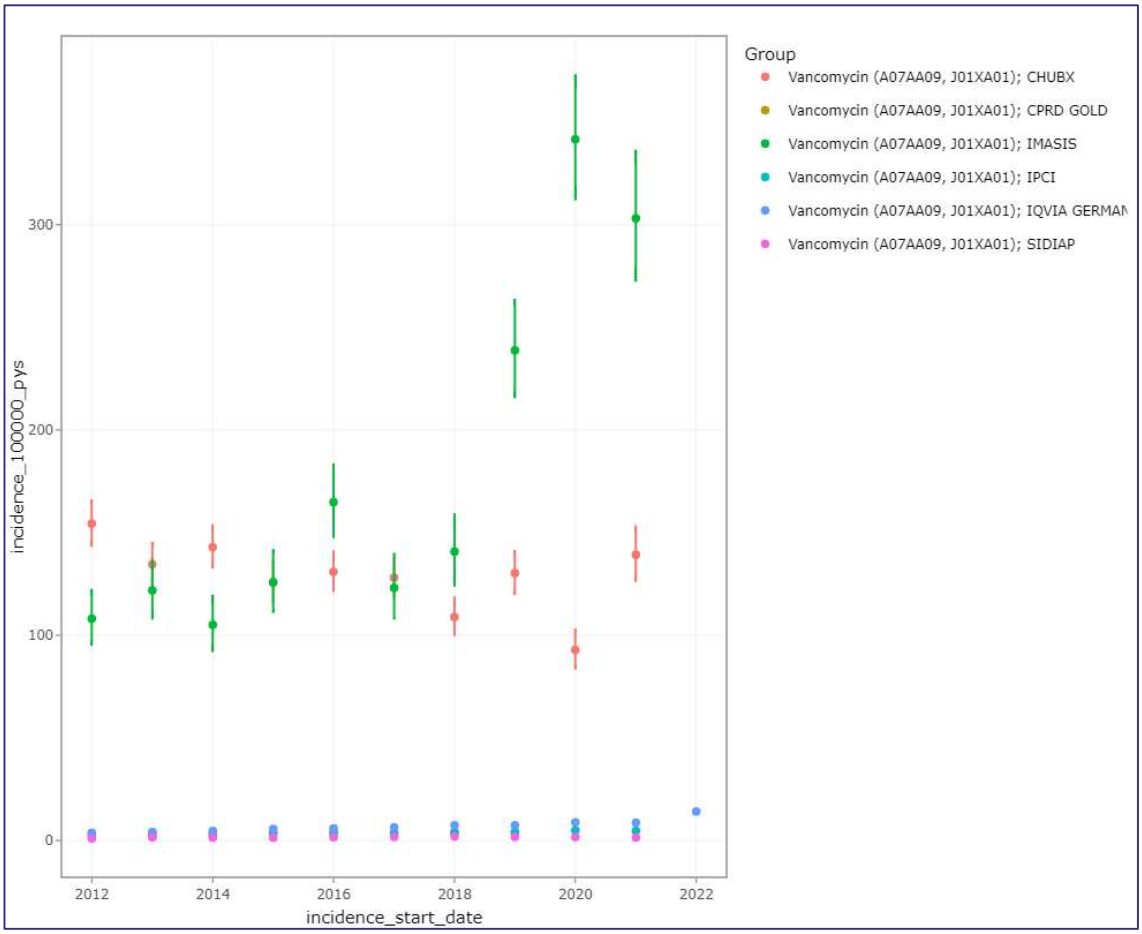


Figure 12.4.1-15: Incidence rates of vancomycin.

The main findings from figures 2 12.4.1-1 to 12.4.1-15 are the following:

An **increase** of the following antibiotics over **time**: **ceftriaxone** (IMASIS and CHUBX), **cefuroxime** (SIDIAP en IMASIS), **piperacilline-tazobactam** (IMASIS and CHUBX) and **vancomycin** (IMASIS). Use of **fosfomycin** increased over time expecially for SIDIAP, IPCI, IMASIS and IQVIA Germany. Use of **azithromycin** increased up to 2018 in SIDIAP and up to 2020 in IMASIS after which it started to decrease again. In IPCI, use of azithromycin decreased from the beginning of the study period whereas it remained stable in CPRD GOLD and CHUBX but use was much lower.

Use of fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin) **decreased or remained stable** over time. Differences in the types of fluoroquinolones being prescribed over the different databases were observed where ofloxacin was mainly prescribed in CHUBX (France) and IQVIA (Germany) whereas use of ciprofloxacin and levofloxacin was lower in France compared to the other databases.

Other antibiotics for which the incidence decreased over time were **pheneticillin** (IPCI), **oxytetracycline** (CPRD GOLD), **erythromycin** (CPRD GOLD) and **clarithromycin** (CPRD GOLD).

Some of the antibiotics were only prescribed in some of the databases like clarithromycin, erythromycin, lymecycline and oxytetracycline which were prescribed in CPRD GOLD but where use in

the other databases was low or non existent. Incidence rates of these drugs in CPRD GOLD decreased over time or remained stable (lymecycline). Pheneticillin was only prescribed in IPCI and use decreased over time. Cefaclor was prescribed in IQVIA Germany whereas use in the other databases was much lower.

Incidence rates of the antibiotics of the WHO Watch list by sex and age groups

Because of the large number of individual antibiotics in the WHO Watch list, information on the incidence rates of antibiotics by sex and age group are presented by antibiotic class and not by individual substance. Results are presented by figures. The tables with information on incidence rates of these antibiotic subclasses by sex and age group can be consulted in the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/).

The classification of the individual antibiotics from the WHO Watch list by class of antibiotics is provided in table 2 of the appendix.

The figures below (Figure 12.4.1-16 to Figure 12.4.1-30) describe the incidence rates of antibiotic subclasses to which the individual antibiotics from the WHO watch list belong. Subclasses with no use (quinolones and phenolderivates) are not presented. In general, **use of antibiotics** belonging to these subclasses **increases with age except for macrolides** where use was high in children, decreased in adults and increased again from the age of 40 on. Use of penicillins was high in IPCI – especially in the young and decreased when getting older whereas in CHUBX, increase of use of penicillins with age was observed. Also use of **second generation cephalosporins** was **high in children and adolescents** (especially in SIDIAP and IQVIA Germany) and decreased up to the age of 50 where it increased again in SIDIAP. **Use of tetracyclines in adolescents and young adults was high** especially in CPRD GOLD and decreased and stabilised from the age of 30 on and then further decreased by age (from the age of 39) especially in women. Finally, although the use of **third generation cephalosporins increased with age**, use of this drugs was also higher in young children than in adolescence, or young adults, especially in secondary care data (IMASIS and CHUBX).

Use of antibiotics was comparable in males compared to females except for Beta lactamase-inhibitor_anti-pseudomonal antibiotics, carbapenem and 4th generation cephalosporins where use was higher in males than in females. For **phosphonics**, the opposite was observed where use was **higher in females than in males**.

For IQVIA Germany, use of aminoglycosides was high in children but this presumably refers to aministration of aminoglycosides as droplets for treatment of eye and/or ear infection.

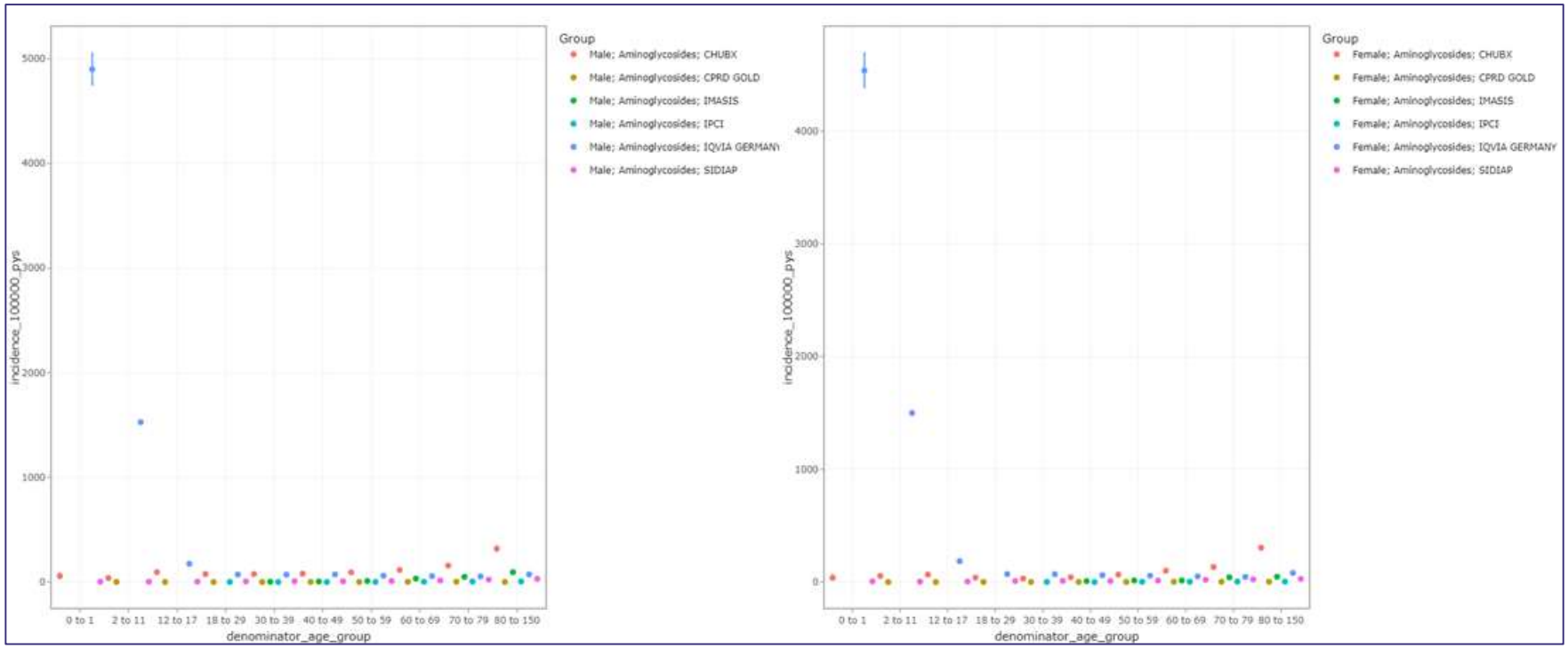


Figure 12.4.1-16: Incidence rates of Aminoglycosides by age and sex.

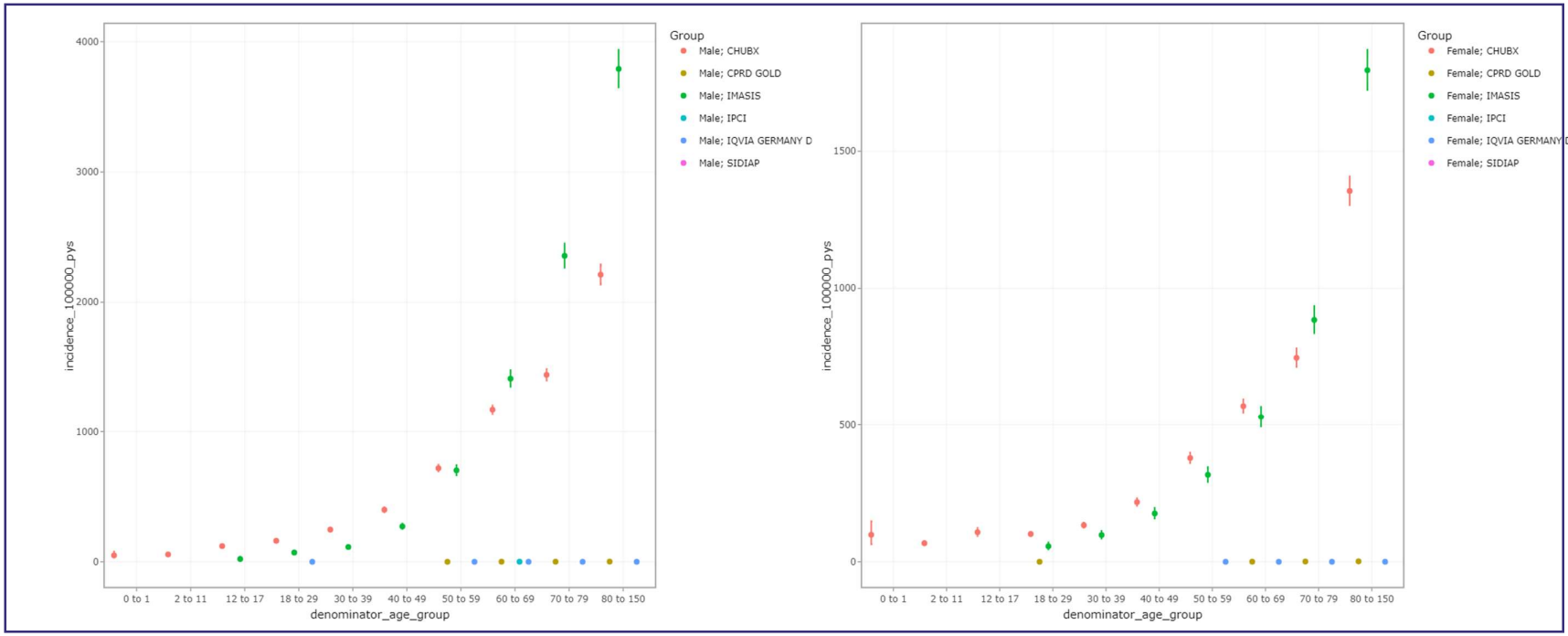


Figure 12.4.1-17: Incidence rates of Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal by age and sex.

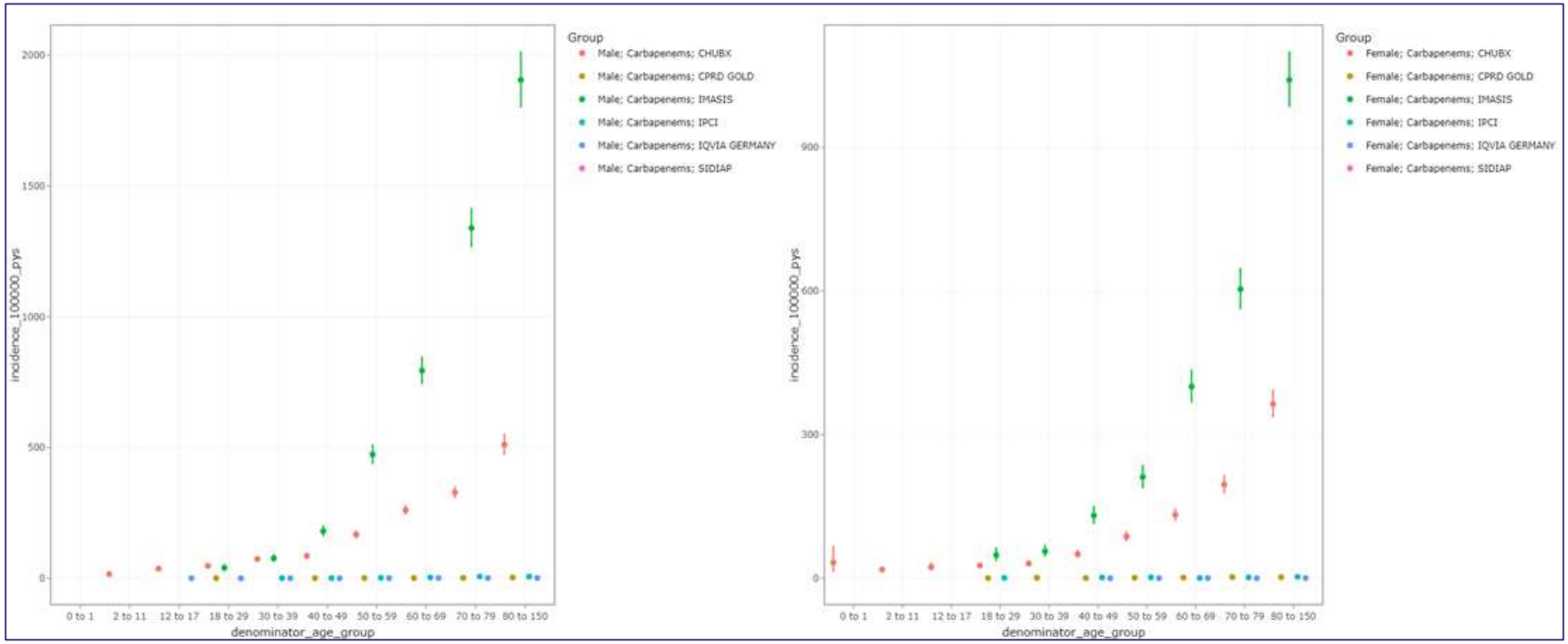


Figure 12.4.1-18: Incidence rates of carbapenem by age and sex.

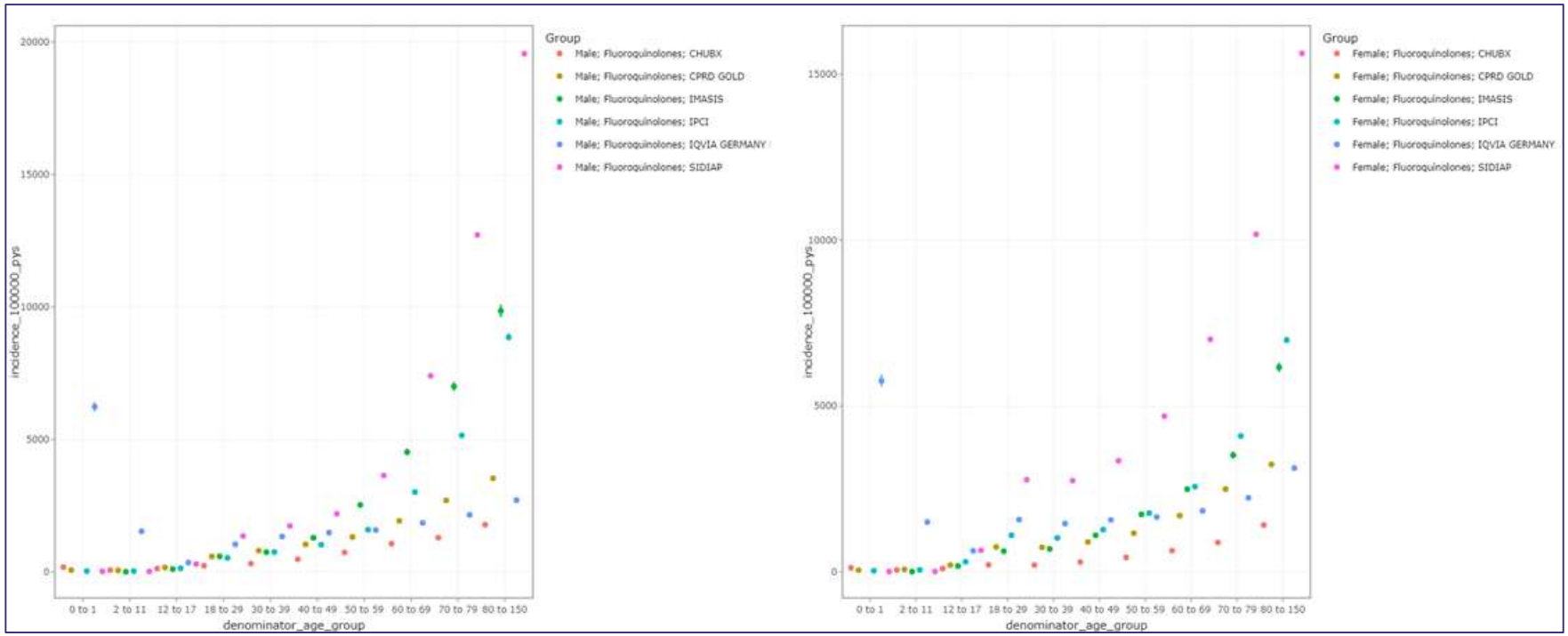


Figure 12.4.1-19: Incidence rates of Fluoroquinolones by age and sex.

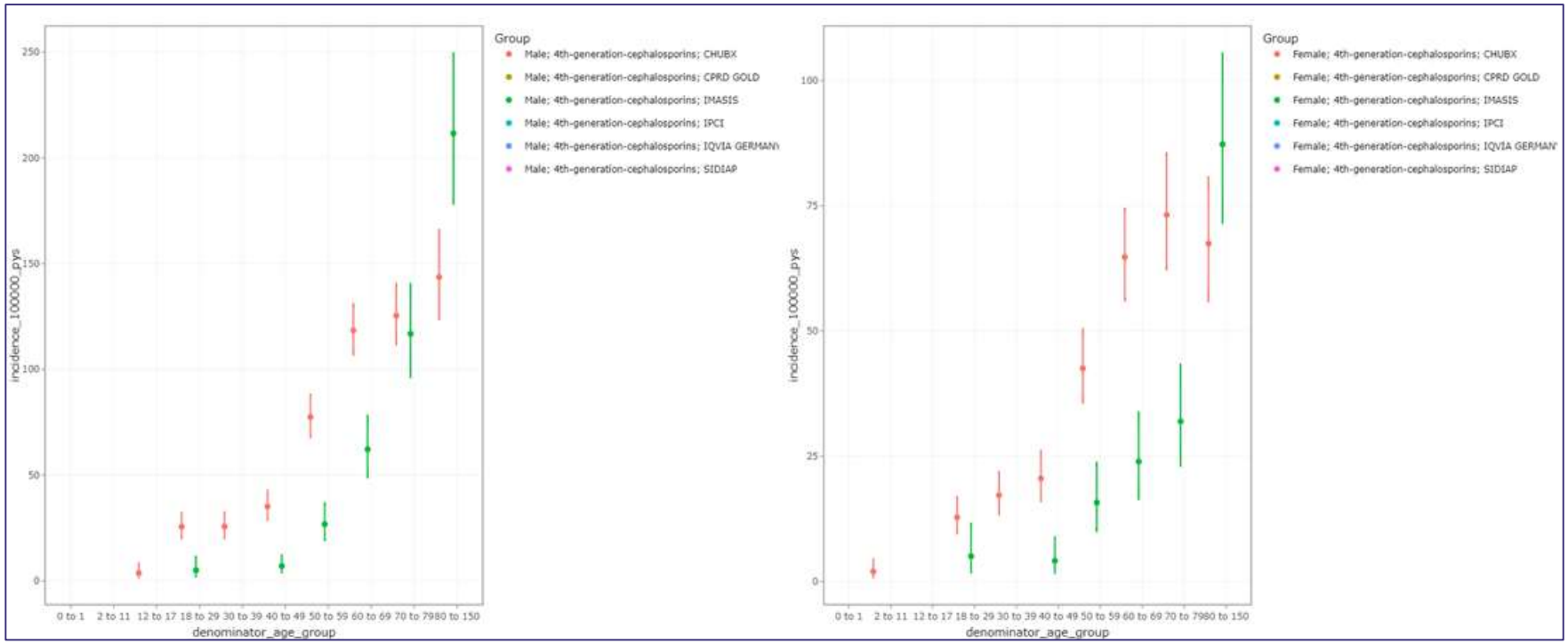


Figure 12.4.1-20: Incidence rates of fourth-generation Cephalosporins by age and sex.

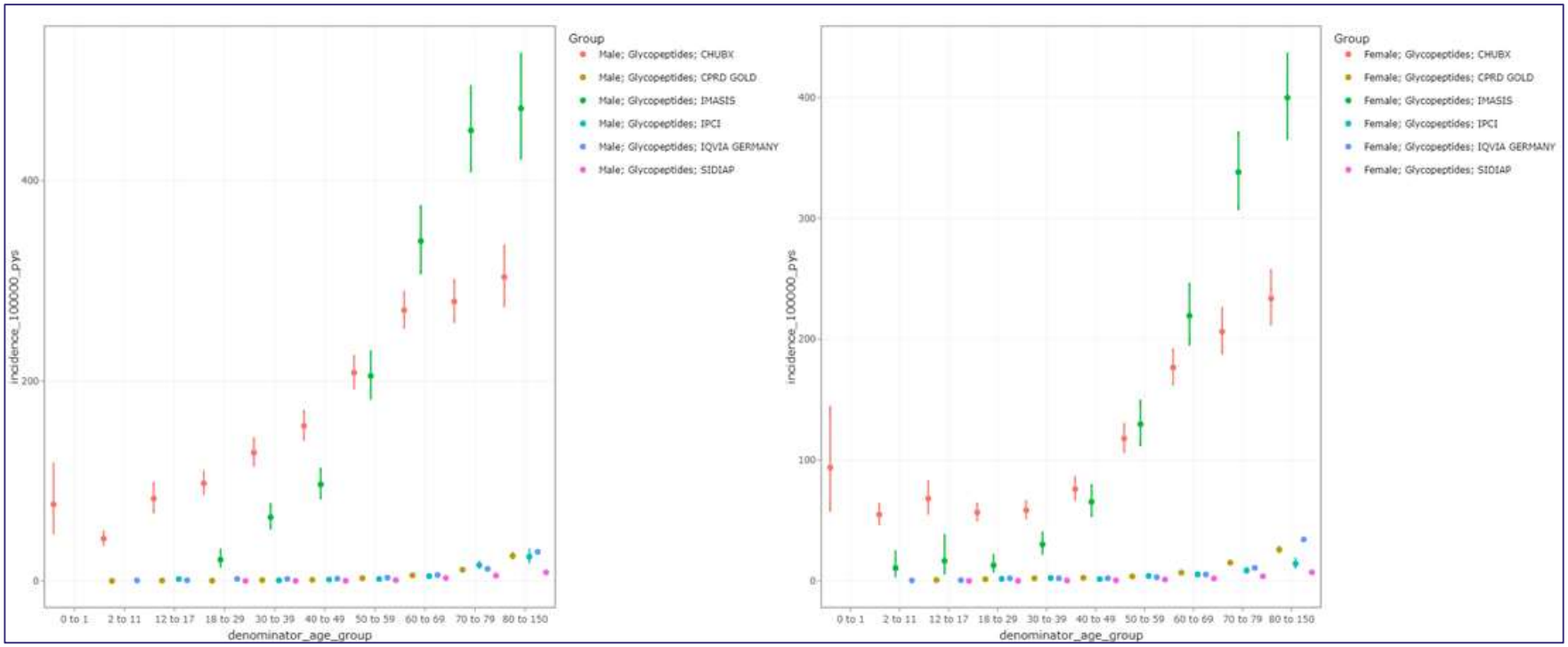


Figure 12.4.1-21: Incidence rates of Glycopeptides by age and sex.

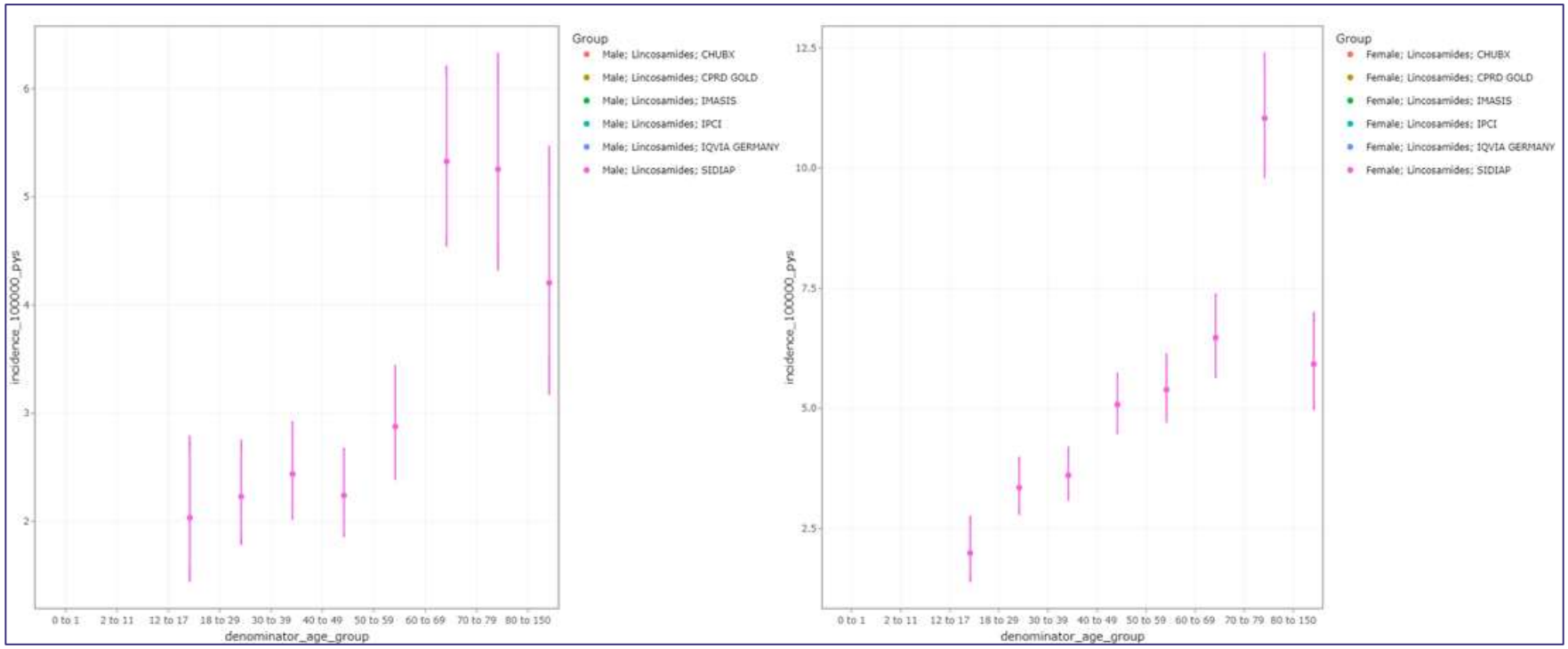


Figure 12.4.1-22: Incidence rates of Lincosamides by age and sex.

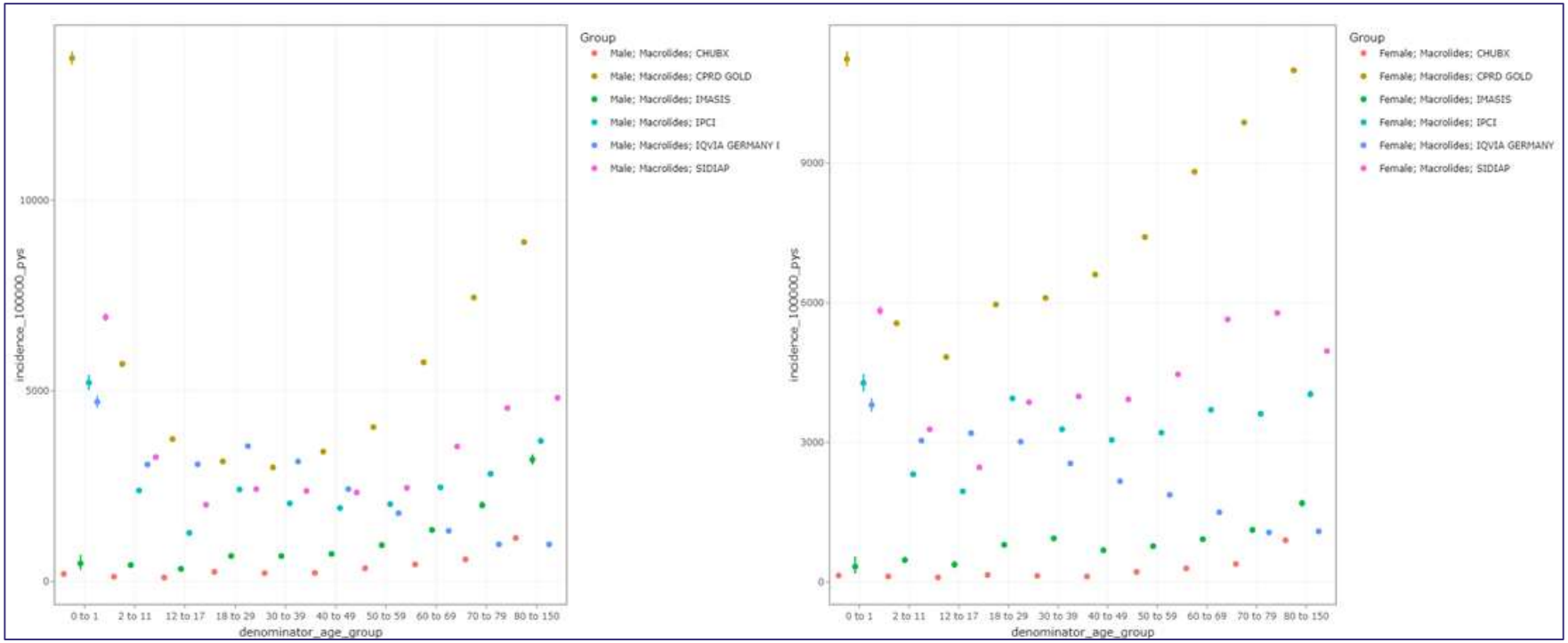


Figure 12.4.1-23: Incidence rates of Macrolides by age and sex.

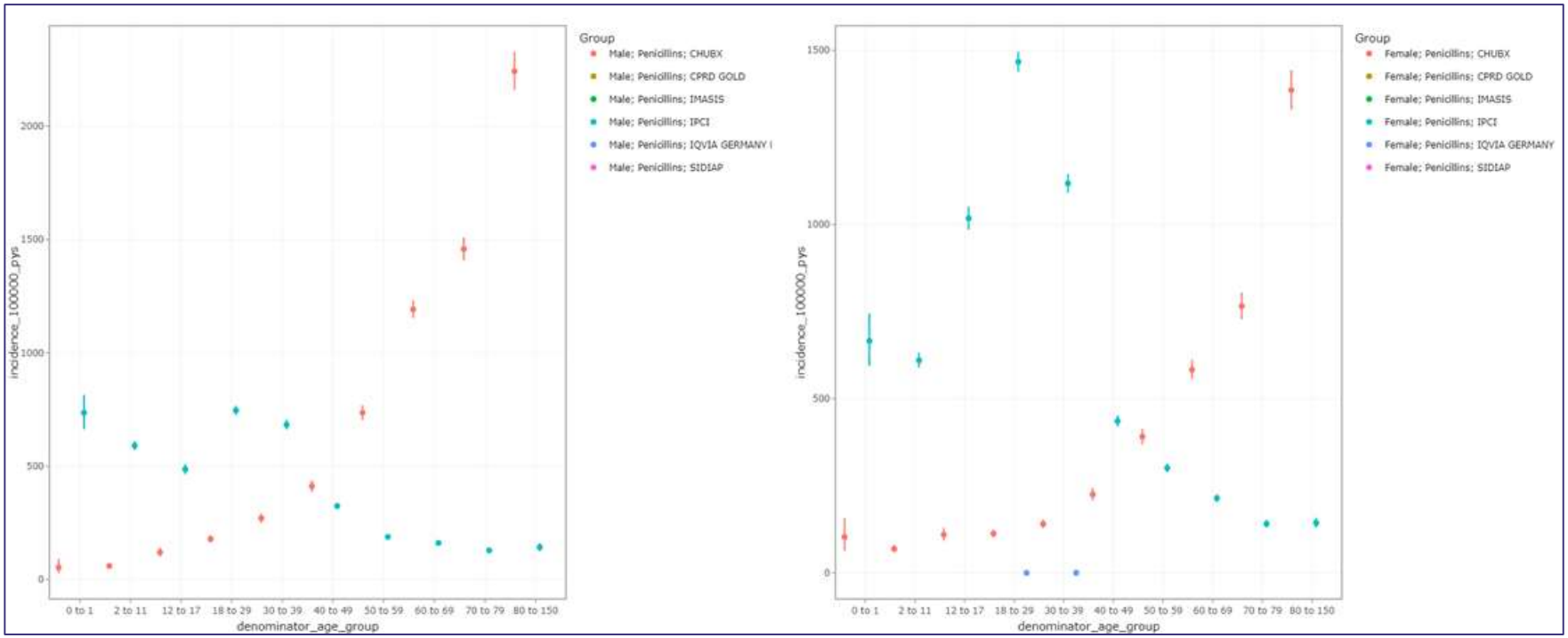


Figure 12.4.1-24: Incidence rates of Penicillins by age and sex.

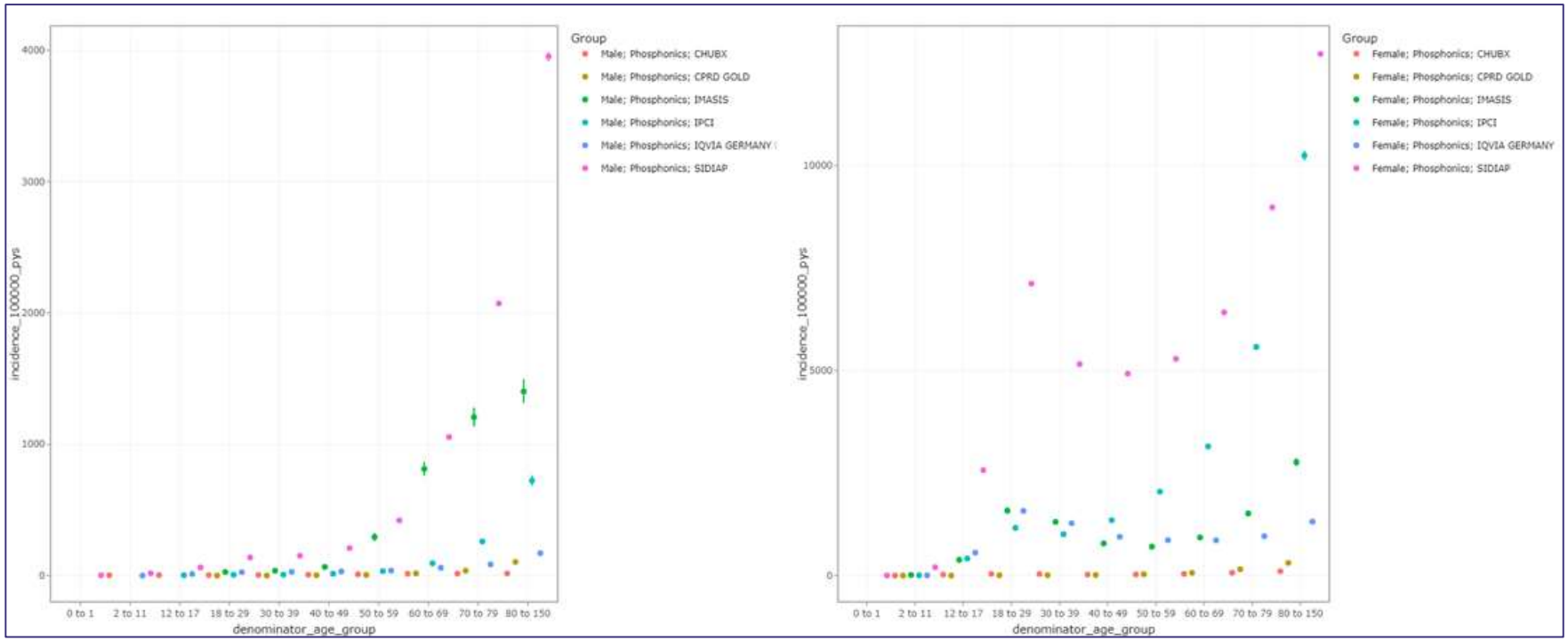


Figure 12.4.1-25: Incidence rates of Phosphonics by age and sex.

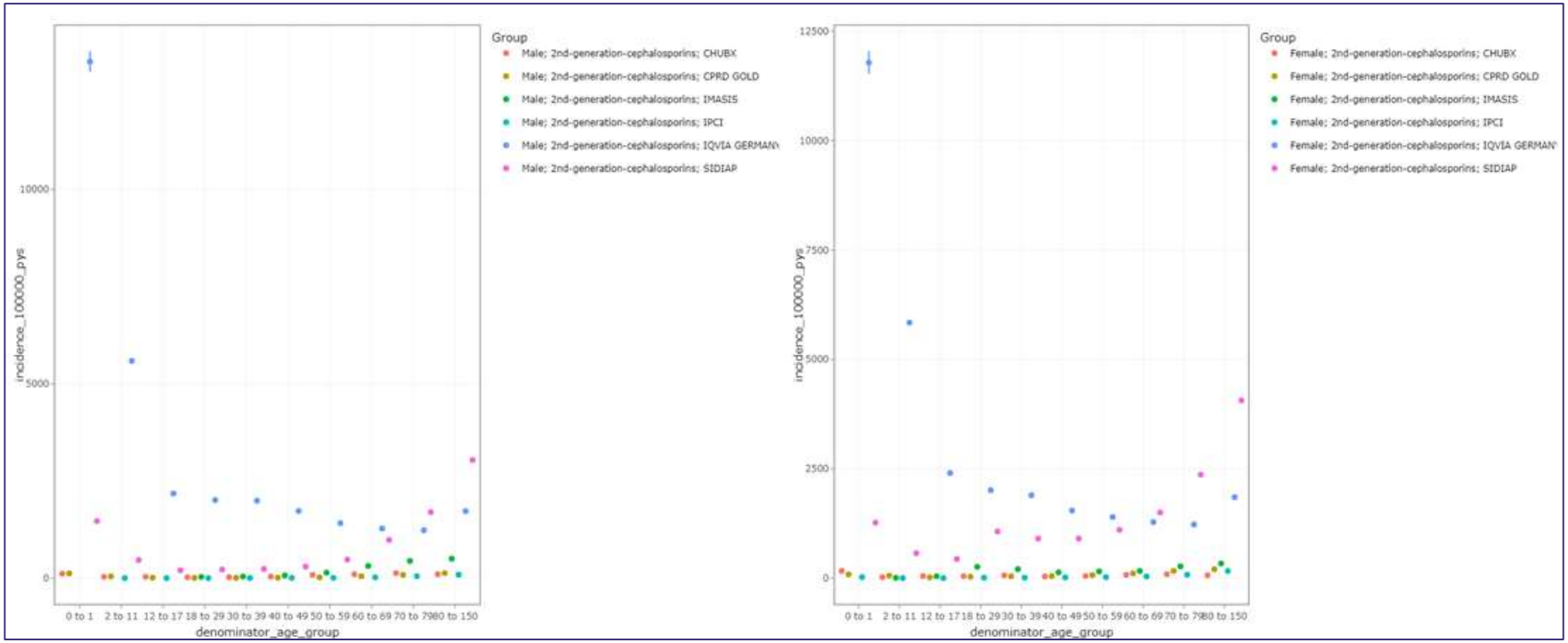


Figure 12.4.1-26: Incidence rates of second-generation Cephalosporins by age and sex.

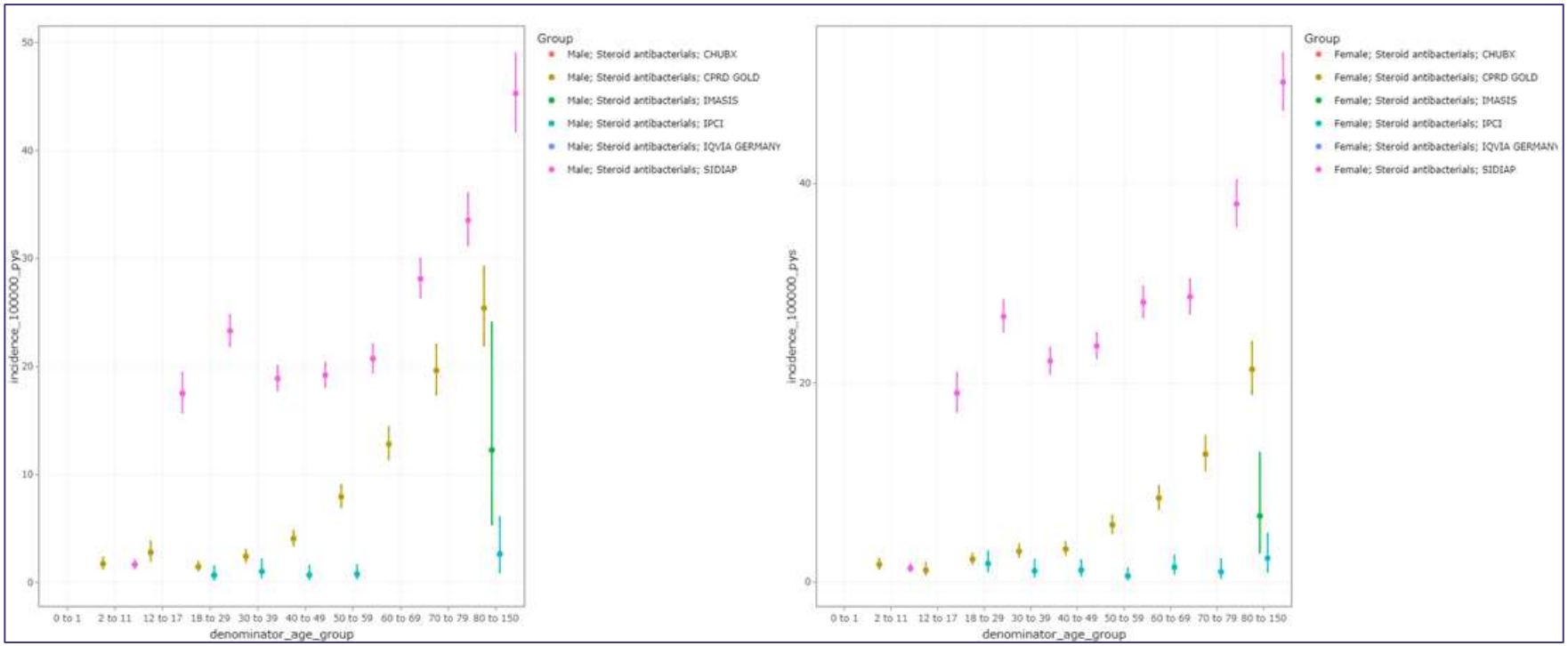


Figure 12.4.1-27: Incidence rates of Steroid Antibacterials by age and sex.

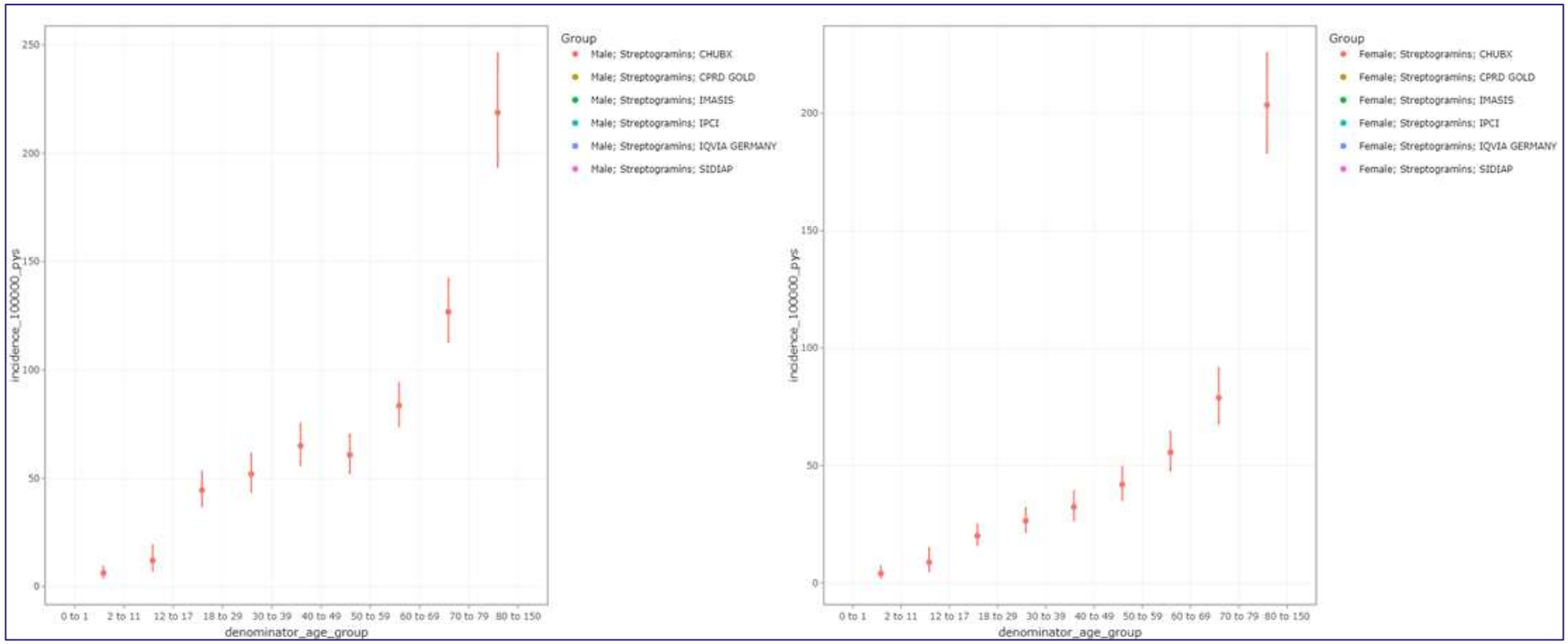


Figure 12.4.1-28: Incidence rates of Streptogramins by age and sex.

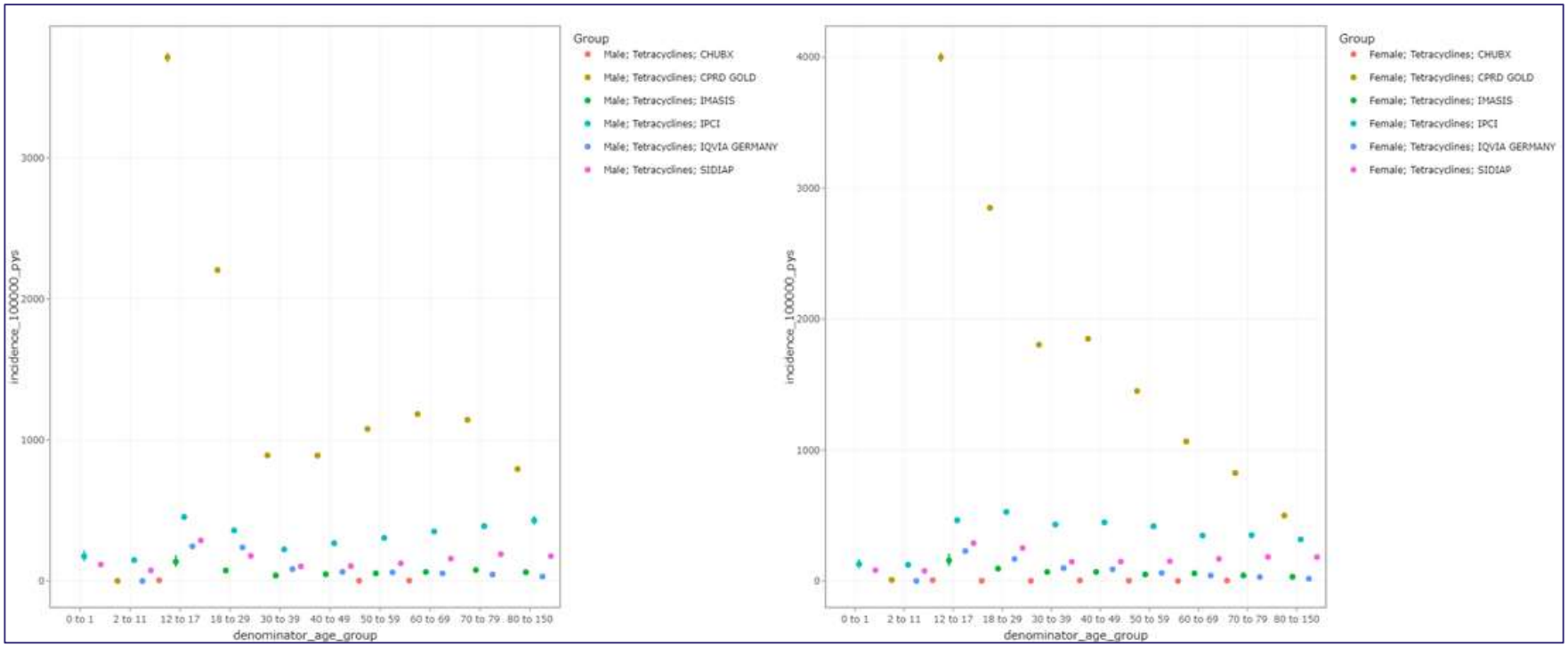


Figure 12.4.1-29: Incidence rates of Tetracyclines by age and sex.

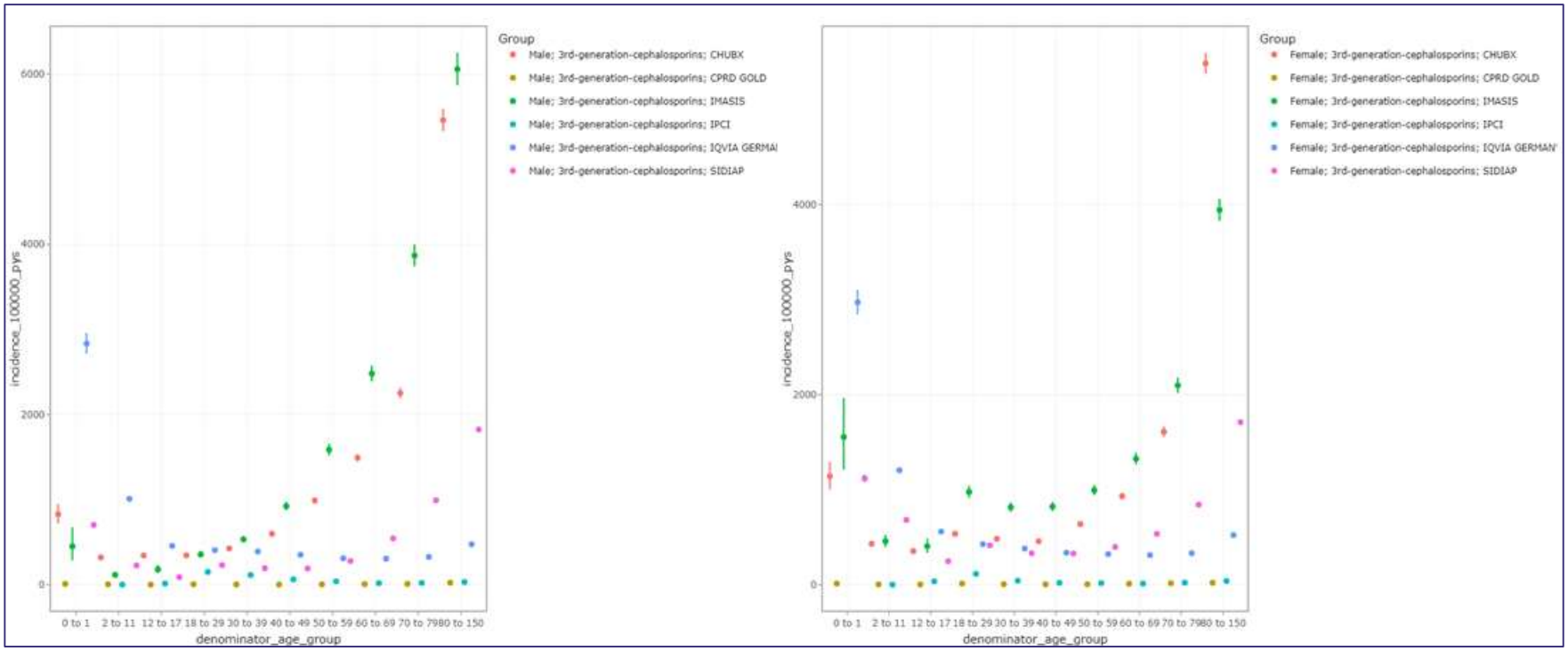


Figure 12.4.1-30: Incidence rates of third-generation-Cephalosporins by age and sex.

Incidence rates of the antibiotics of the WHO Watch list by route of administration

For those databases where antibiotics were mapped to the clinical drug level (all databases except for CHUBX), stratification by type of administration was possible. These data can be consulted via the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/).

As could be anticipated, parenteral use is much higher in secondary care databases (IMASIS) compared to primary care databases (CPRD GOLD, IPCI, SIDIAP and IQVIA Germany) where use of parenteral drugs was less than 50/100.000 PY for those drugs that can be parenterally administered in primary care.

Prevalence of the antibiotics of the WHO Watch list

The proportion of individuals using an antibiotic by calendar year and database can be consulted via the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/). Because of the high number of individual antibiotics, not all antibiotics are described in detail. The figures below (Figure 12.4.1-31 to 12.4.1-45) provide information on the prevalence of those antibiotics where incidence rates belonged to the top 5 of highest incidence rates by database. (see Table 12.1.4-1). Results on prevalence of antibiotic use very much mirror the results on the incidence rates of antibiotic use due to mostly short-term use of antibiotics and limited repetitions of use during one year.

The prevalence was the highest for azithromycin with the highest prevalence for SIDIAP (maximum 3.0% in 2017) and the lowest prevalence in CHUBX (<0.05%). The prevalence of ciprofloxacin was the highest in SIDIAP (2.1% in 2017 and the lowest in CHUBX (0.2% in 2012 – 0.2% 2021). Also clarithromycin was often prescribed with the highest prevalence in CPRD GOLD (3.1% in 2012 – 2.4% in 2019) and lowest prevalence in CHUBX (<0.05%). Also fosfomycin was frequently prescribed with a prevalence of 0.7% in SIDIAP in 2012 and 3.6% in SIDIAP in 2021.

In line with previous results on the incidence rates an increase of the prevalence of the following antibiotics over time was observed for ceftriaxone (IMASIS and CHUBX), cefuroxime (SIDIAP en IMASIS), piperacilline-tazobactam (CHUBX) and vancomycin (IMASIS). The prevalence of fosfomycin increased over time expecially for SIDIAP, IPCI an IMASIS. Use of azithromycin increased up to 2018 in SIDIAP and up to 2020 in IMASIS after which it started to decrease again. In IPCI, use of azithromycin decreased from the beginning of the study period.

No increase of the use of fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin) was observed where the prevalence either decreased or remained stable over time. Differences in the choice of fluoroquinolones being prescribed over the different databases were observed where ofloxacin was mainly prescribed in CHUBX (France) whereas use of ciprofloxacin and levofloxacin was much lower in France compared to the other databases.

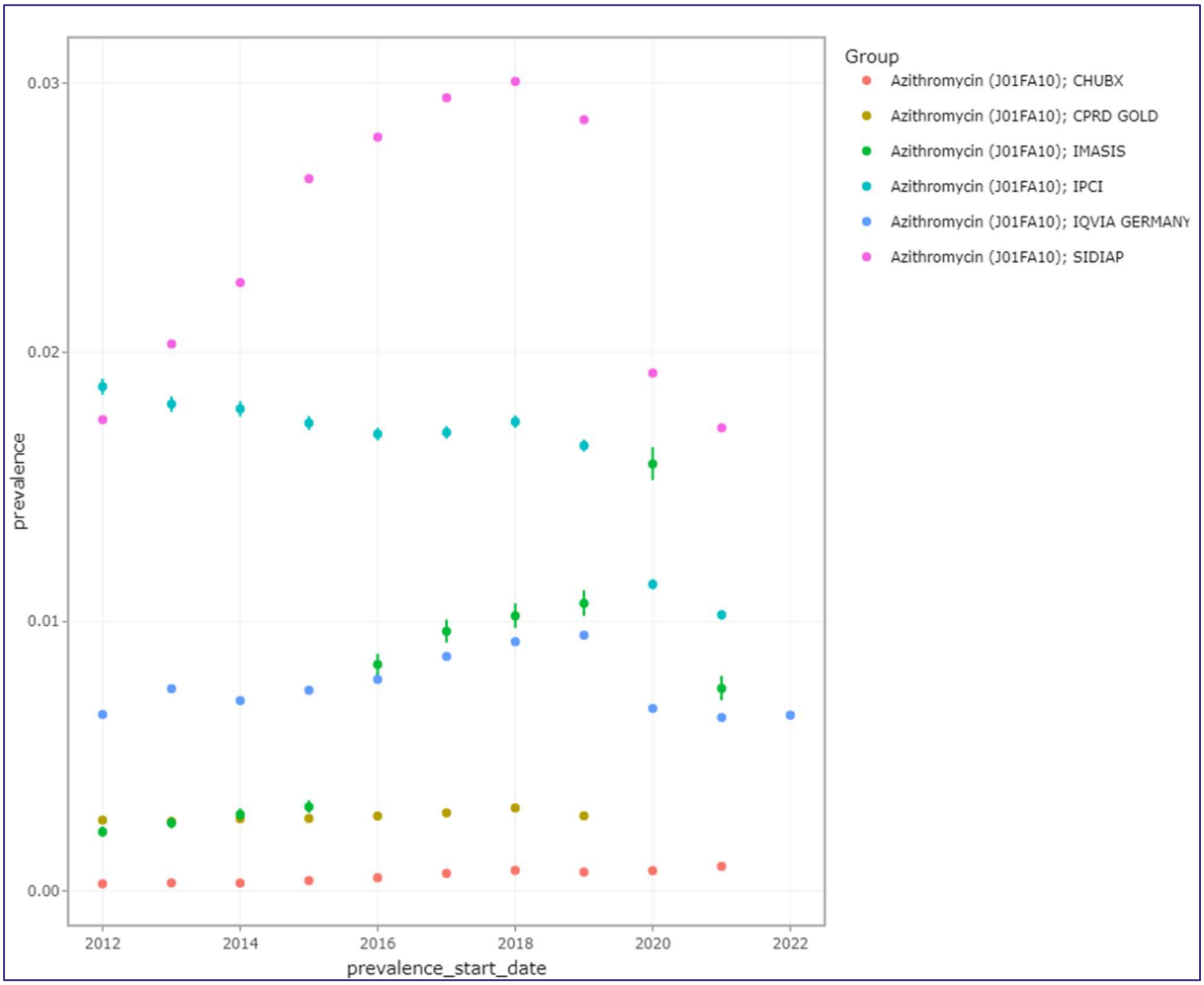


Figure 12.4.1-31: Prevalence of azithromycin.

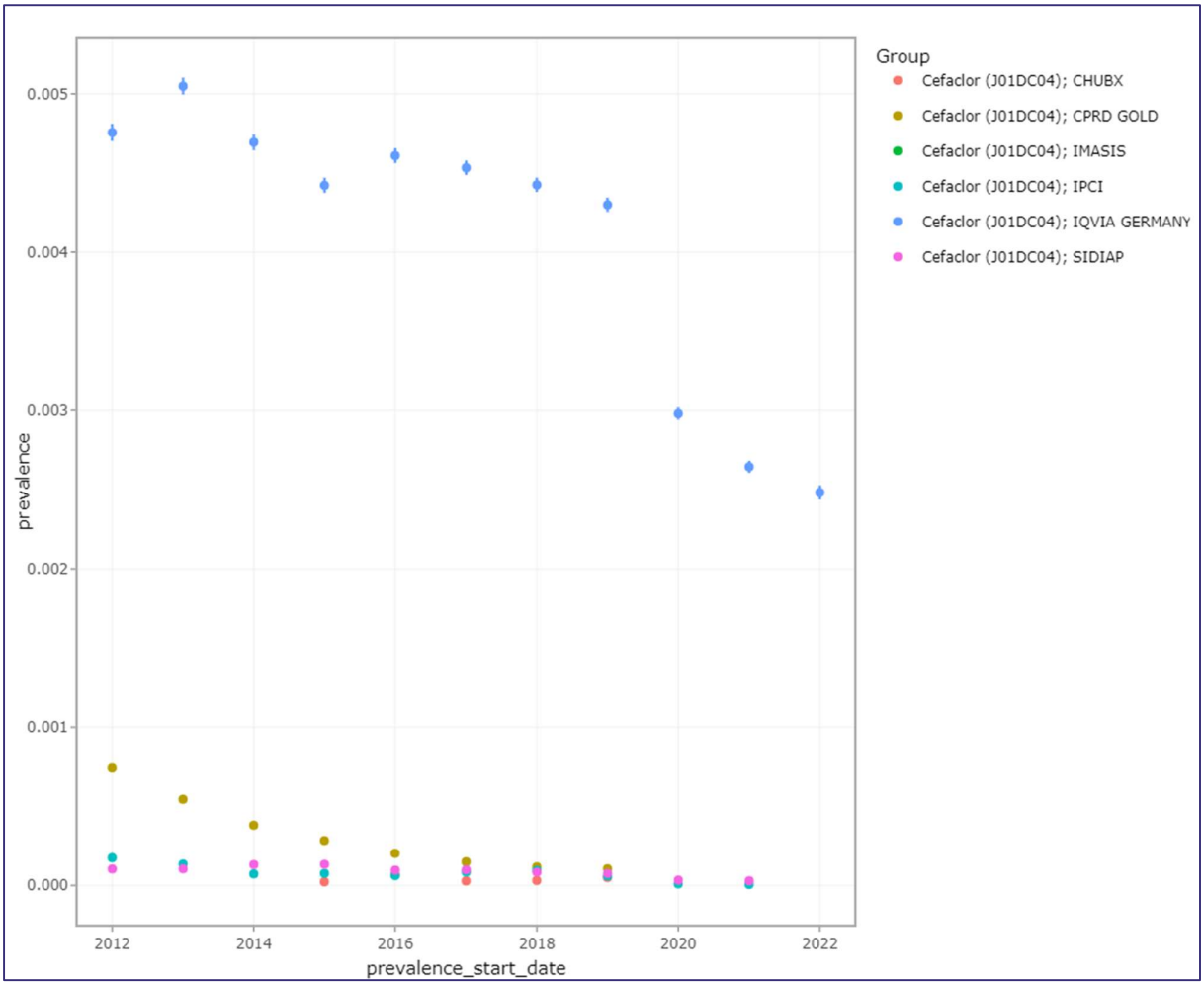


Figure 12.4.1-32: Prevalence of cefaclor.

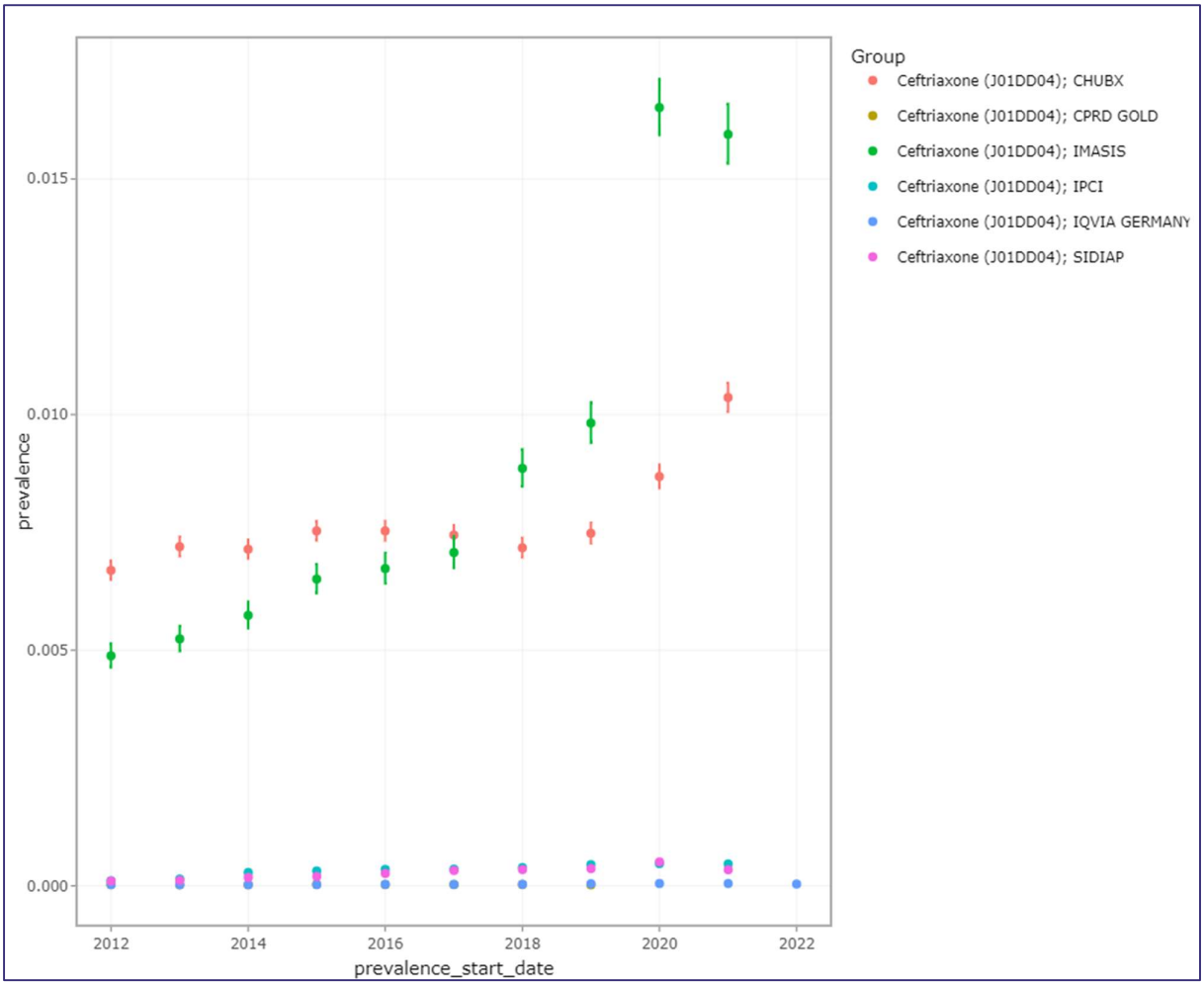


Figure 12.4.1-33: Prevalence of ceftriaxone.

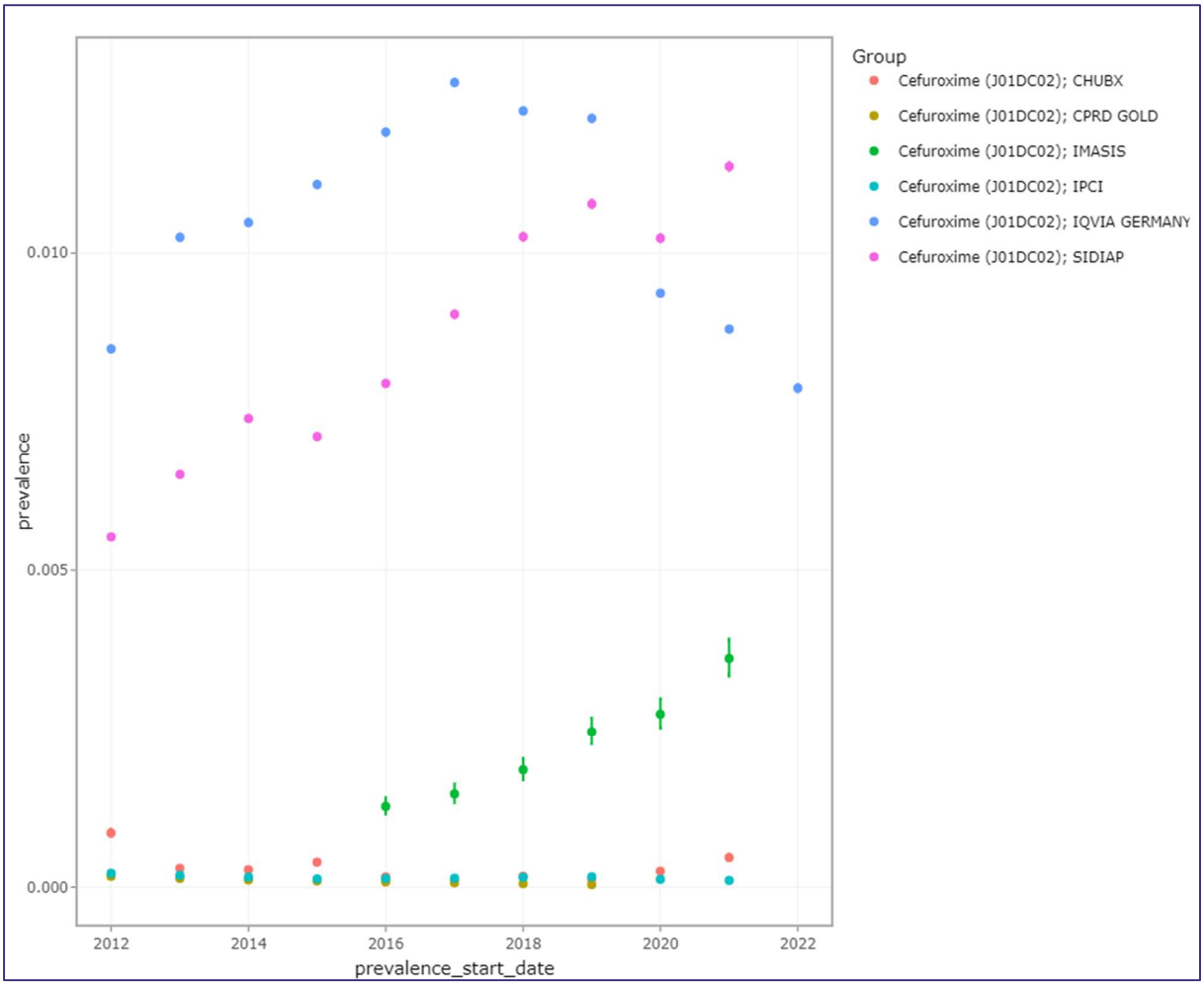


Figure 12.4.1-34: Prevalence of cefuroxime.

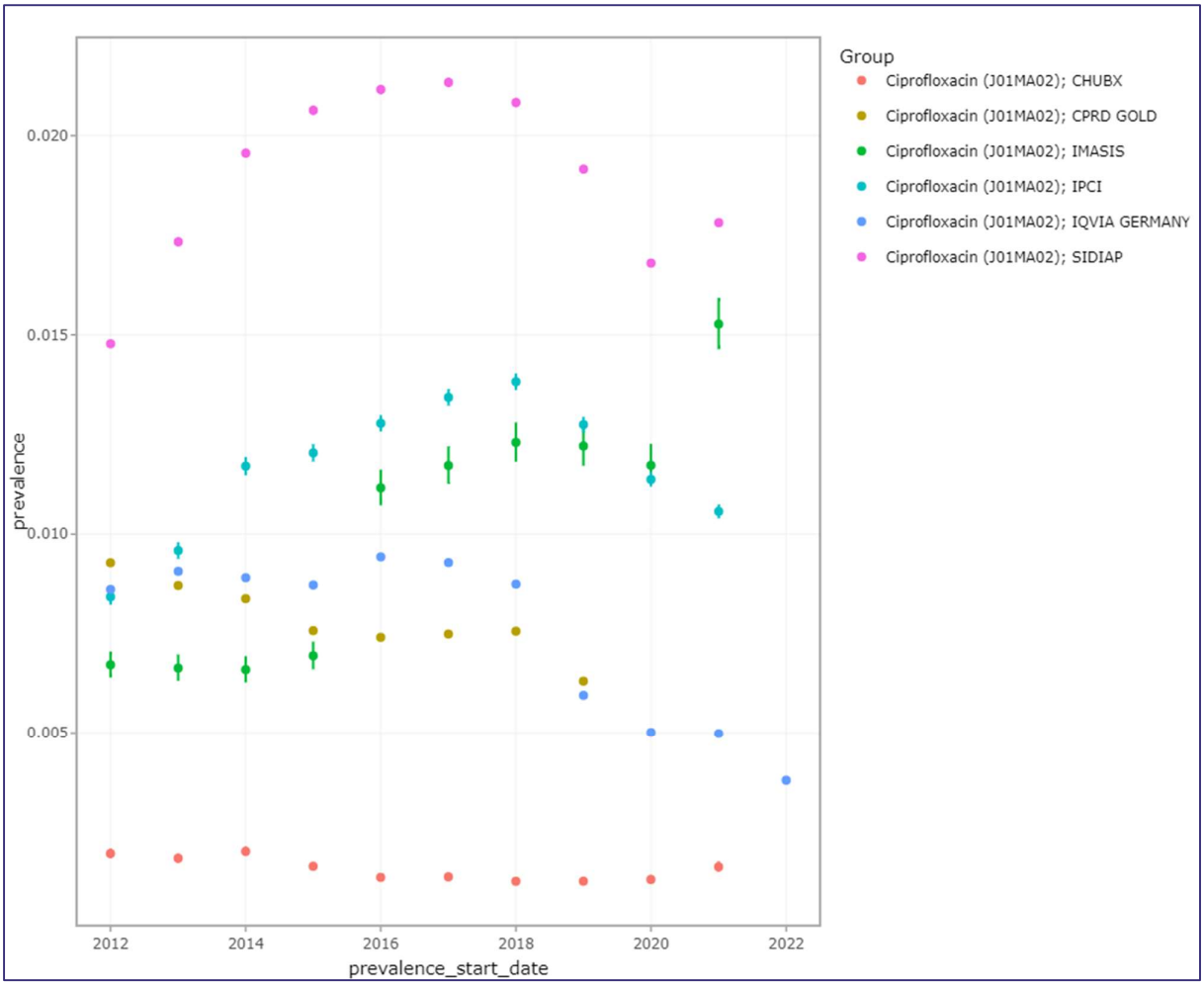


Figure 12.4.1-35: Prevalence of ciprofloxacin.

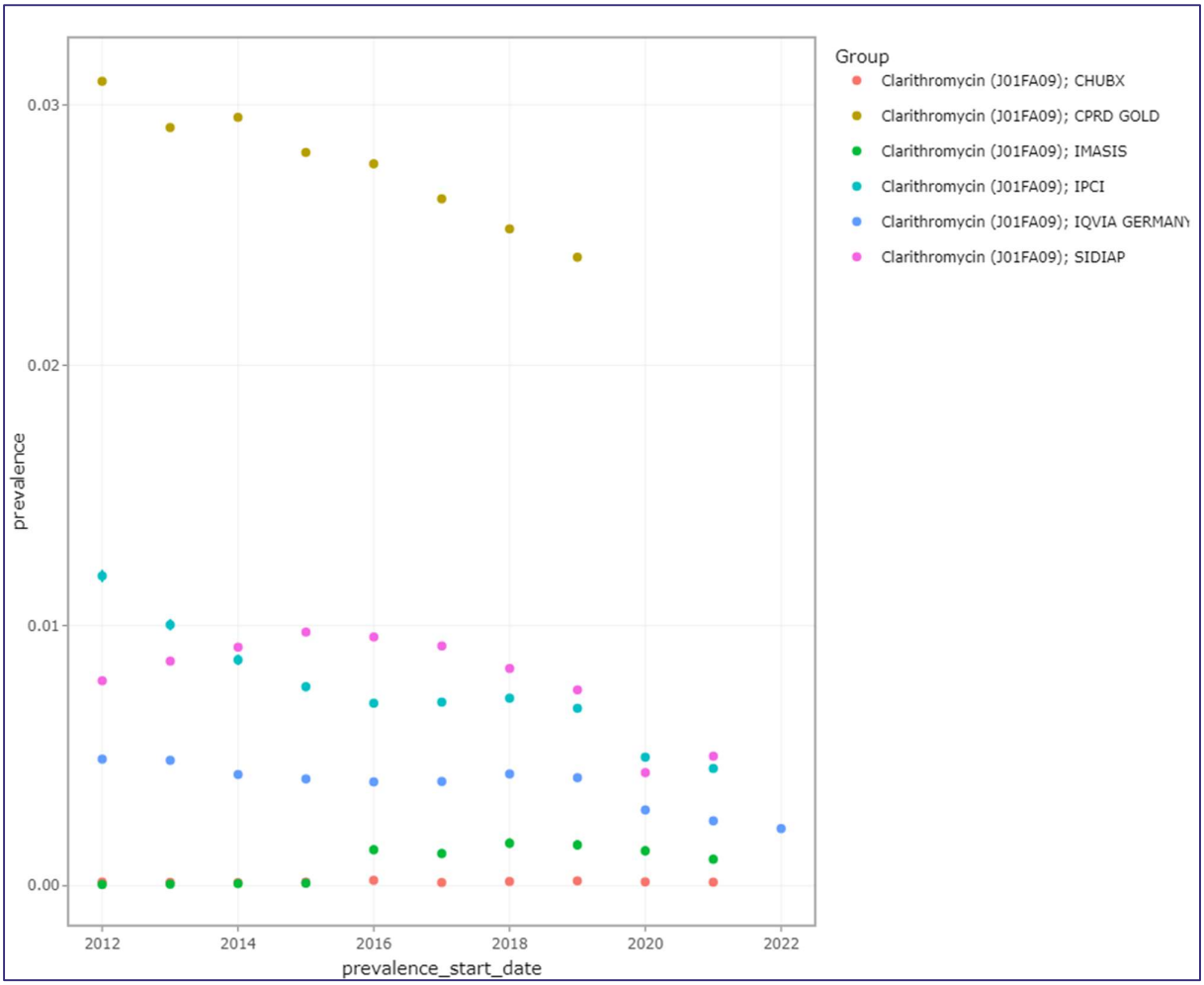


Figure 12.4.1-36: Prevalence of clarithromycin.

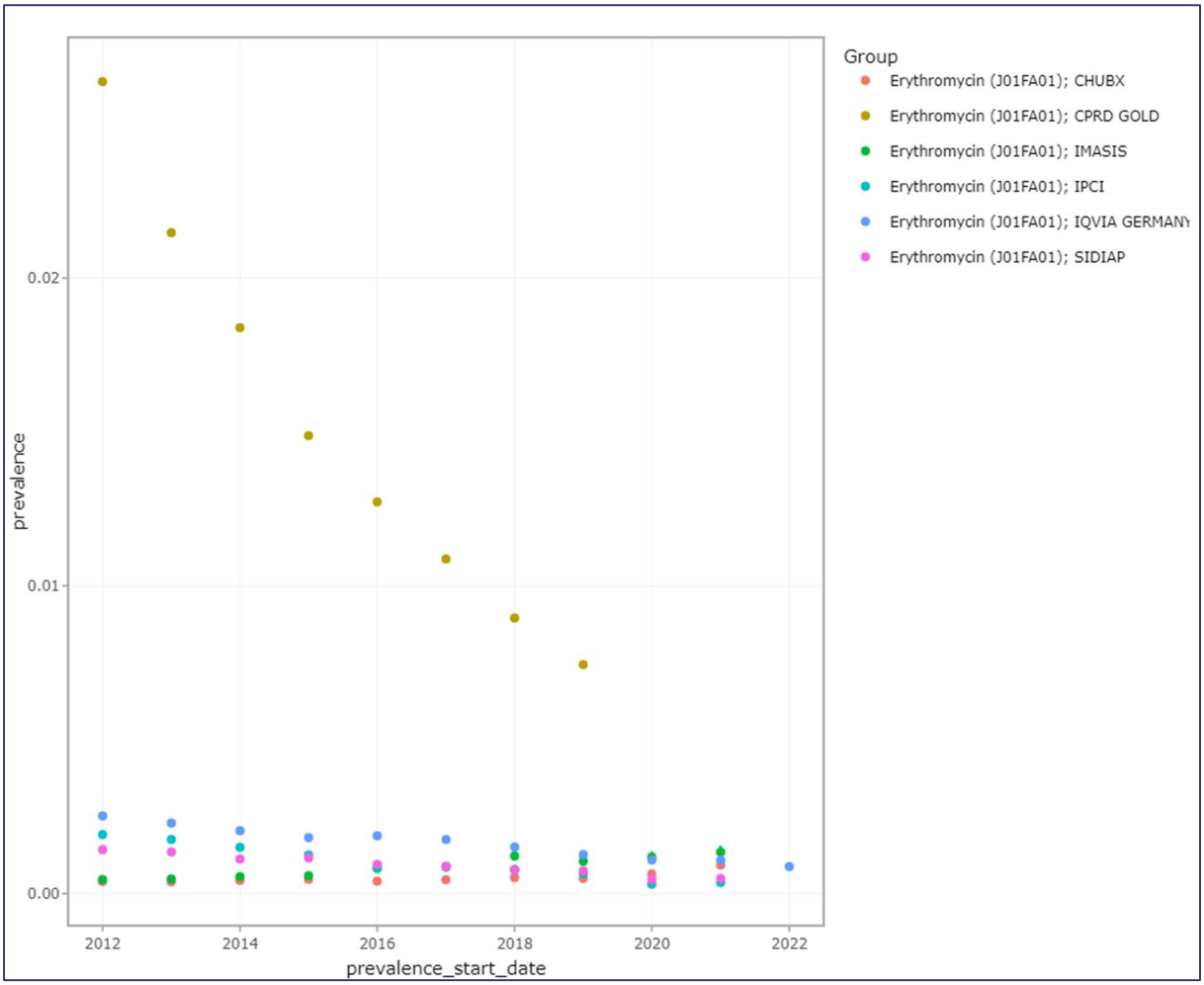


Figure 12.4.1-37: Prevalence of erythromycin.

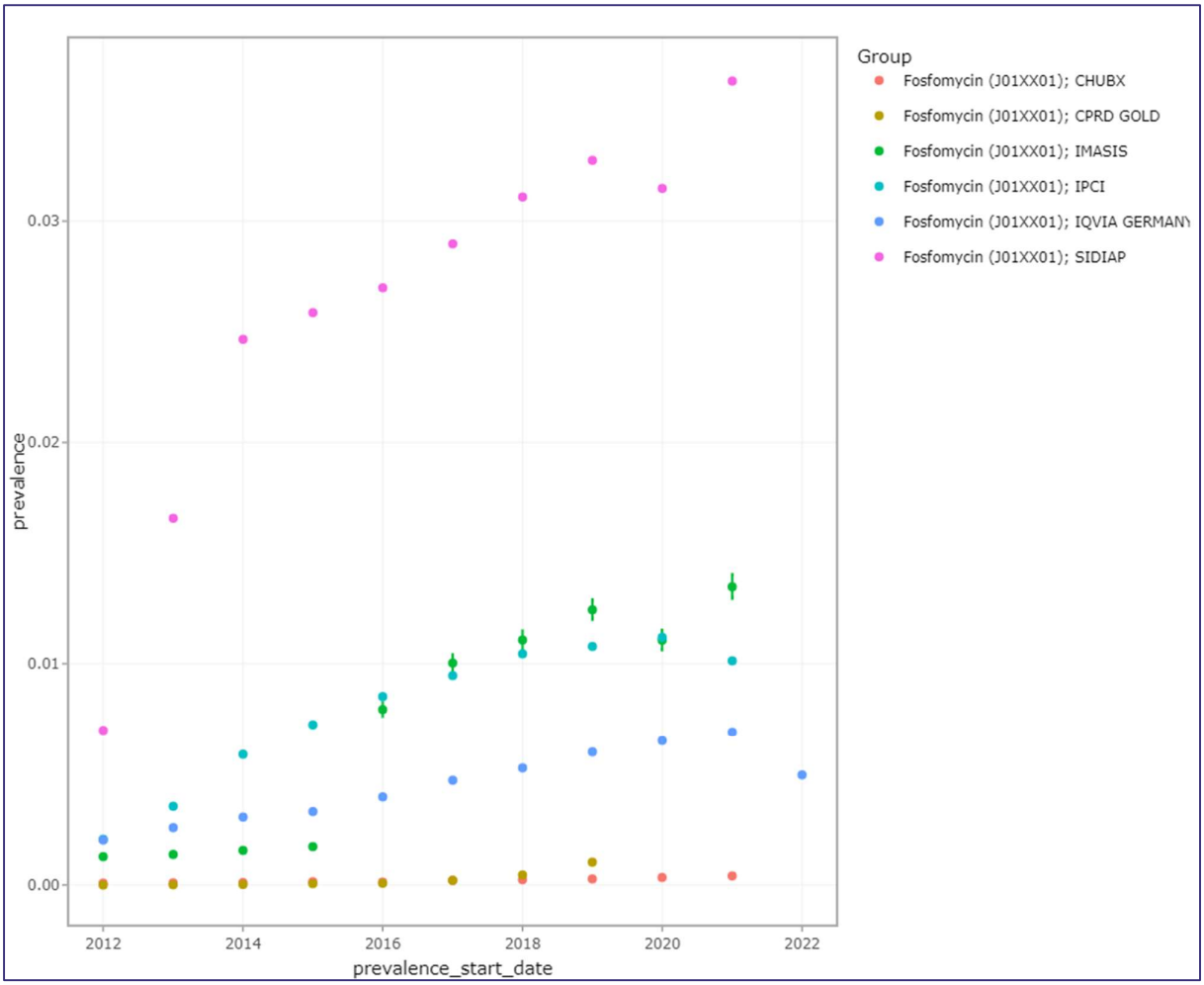


Figure 12.4.1-38: Prevalence of fosfomycin.

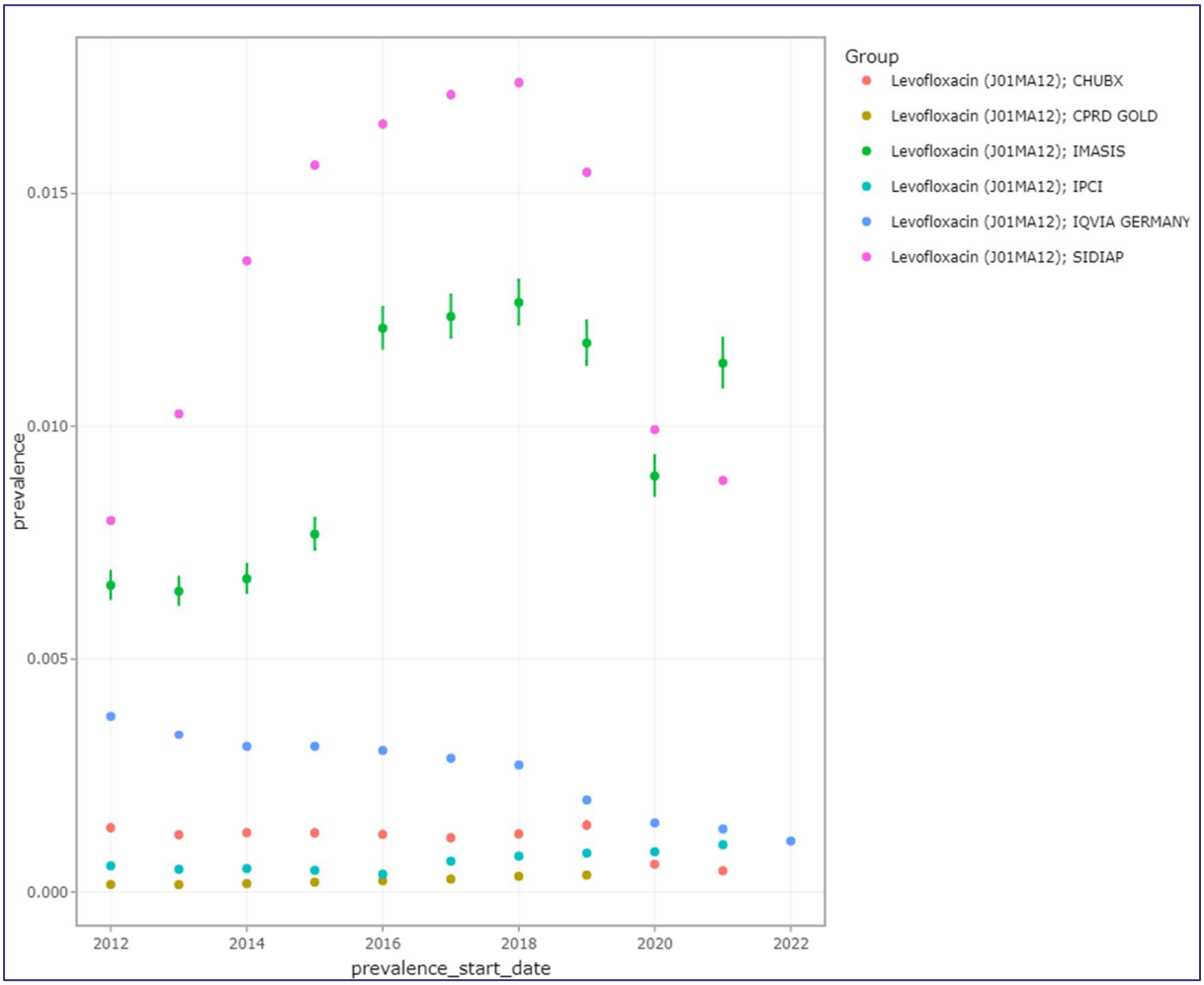


Figure 12.4.1-39: Prevalence of levofloxacin.

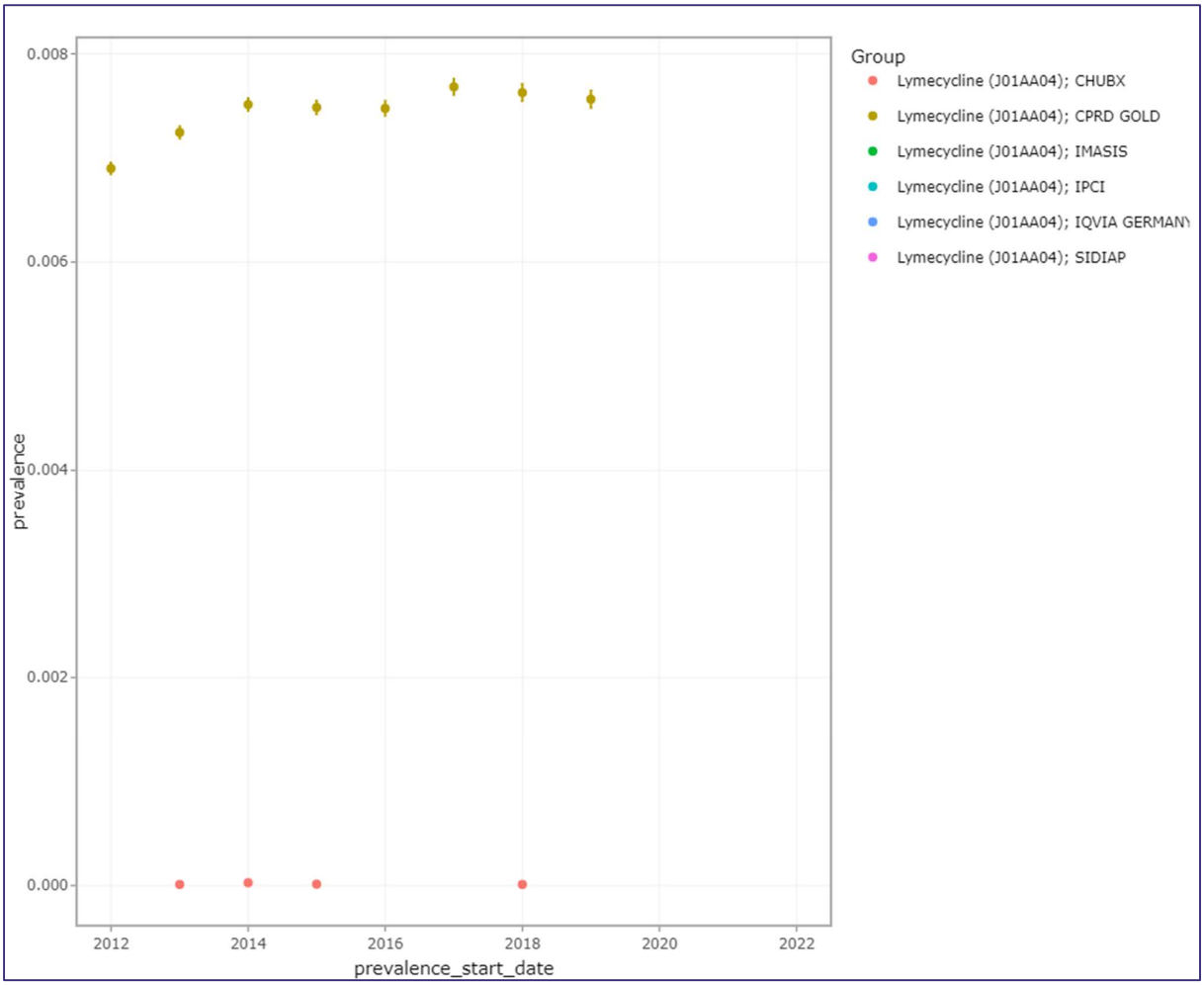


Figure 12.4.1-40: Prevalence of lymecycline.

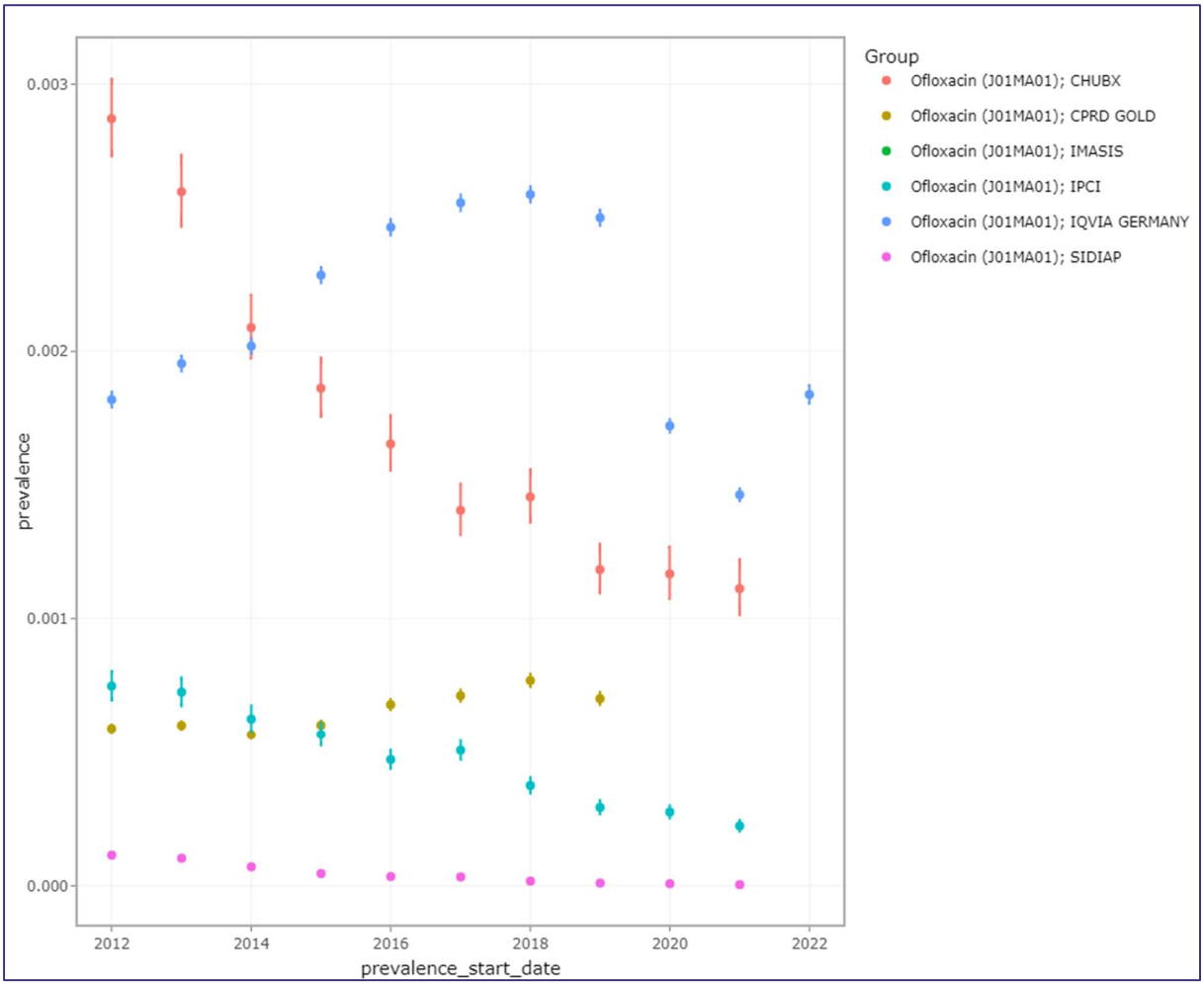


Figure 12.4.1-41: Prevalence of ofloxacin.

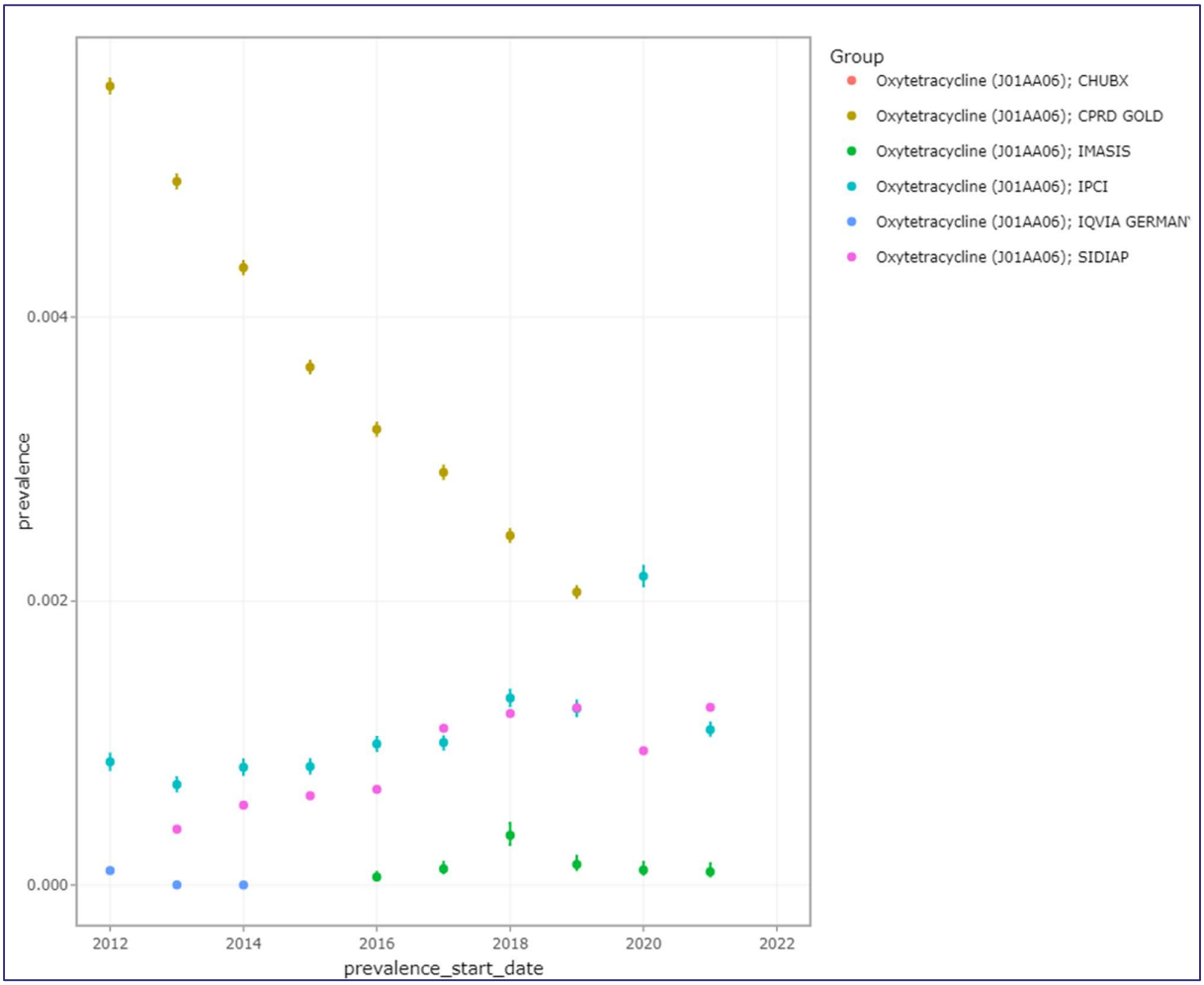


Figure 12.4.1-42: Prevalence of oxytetracycline.

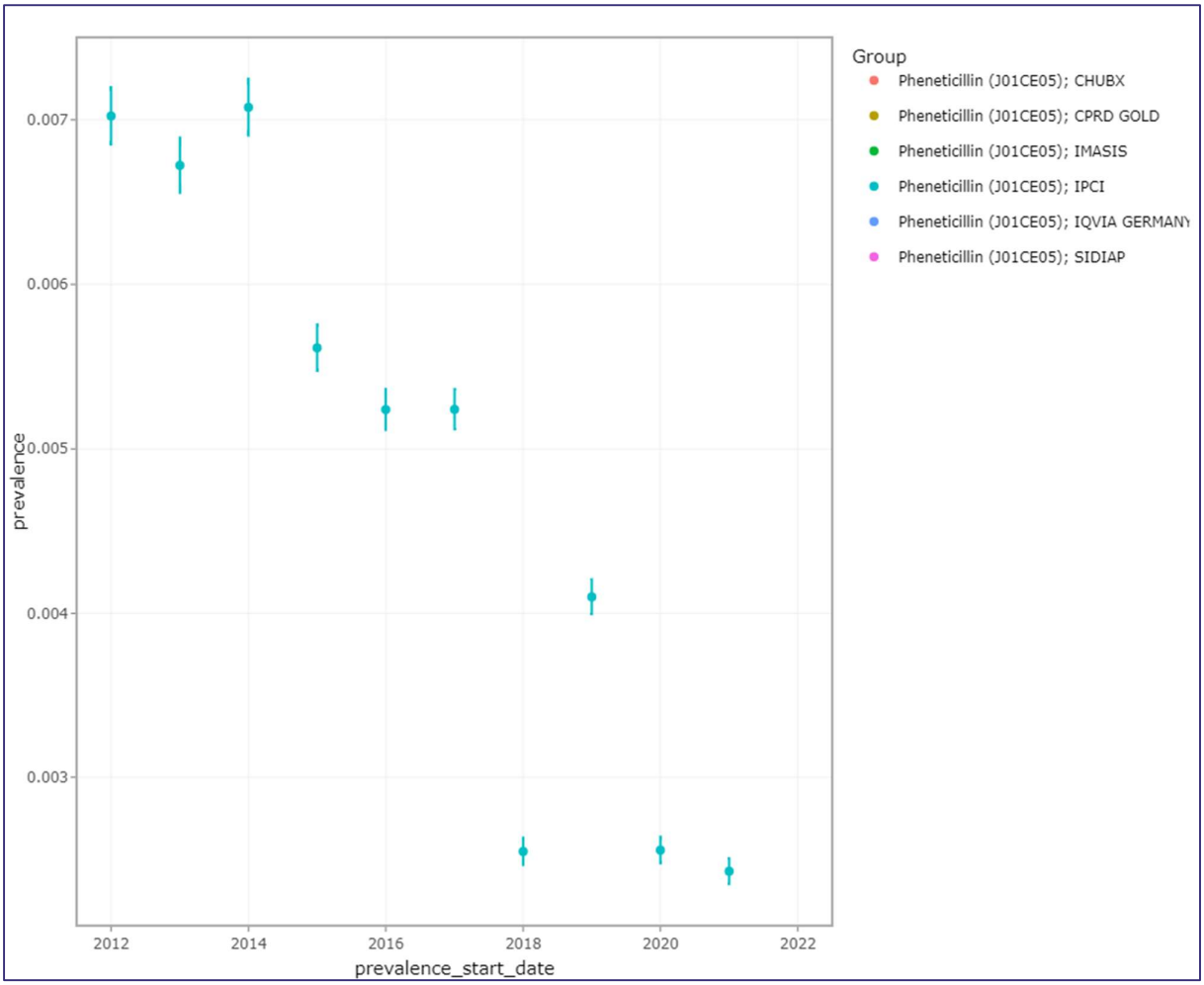


Figure 12.4.1-43: Prevalence of pheneticillin.

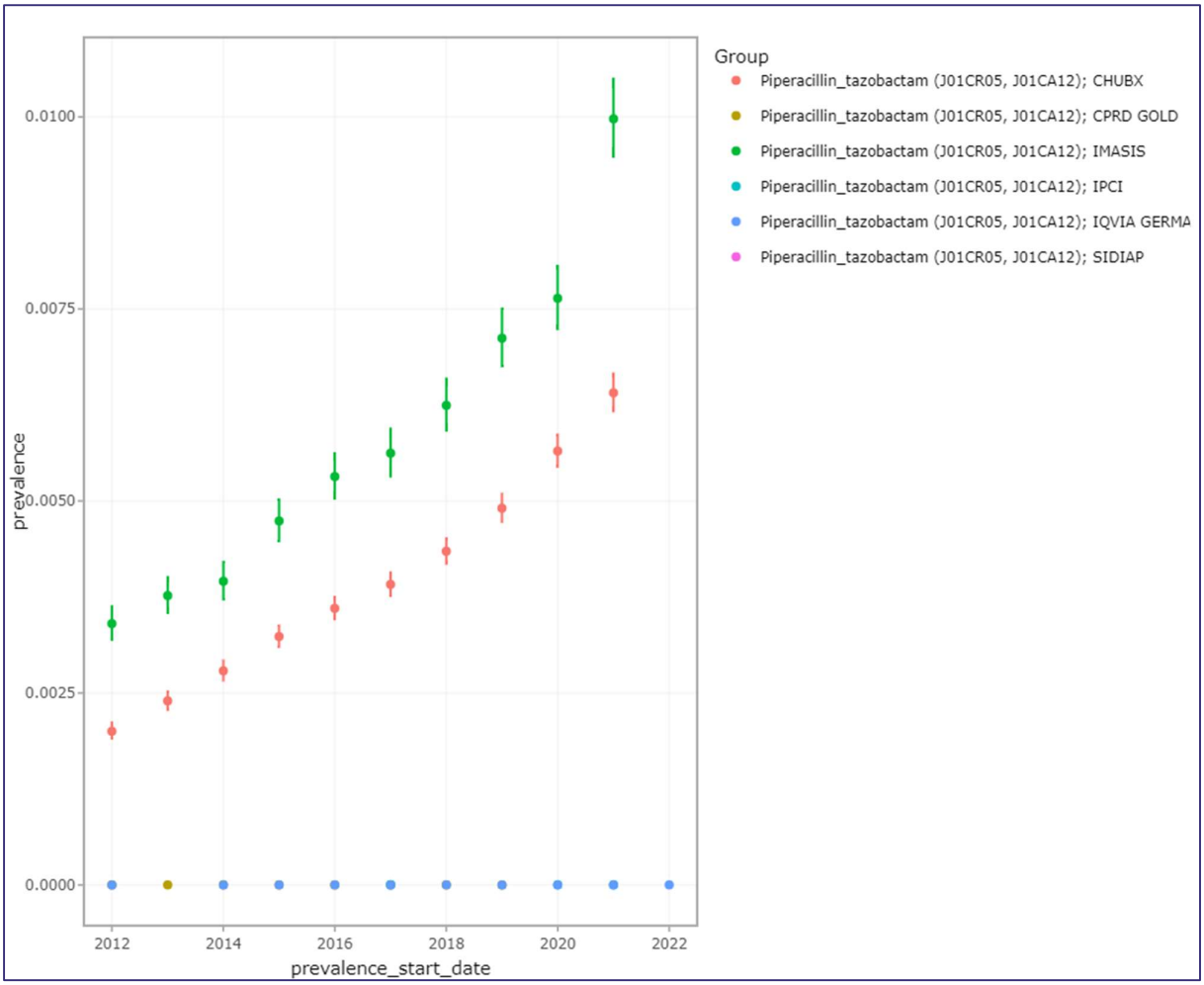


Figure 12.4.1-44: Prevalence of piperacillin tazobactam.

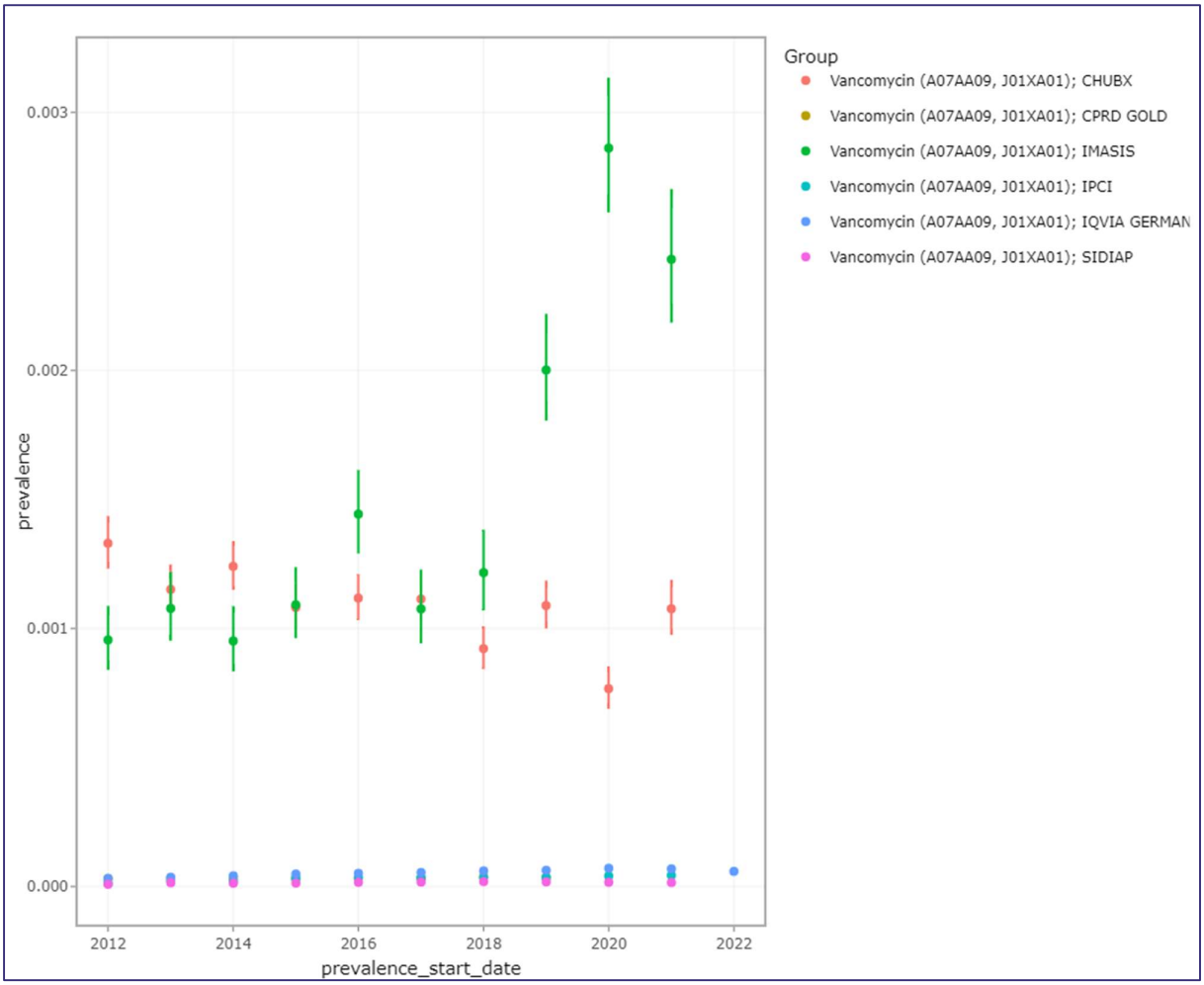


Figure 12.4.1-45: Prevalence of vancomycin.

12.2. Patient-level DUS

The patient level DUS focuses on the duration of use and the indication of use for antibiotics prescribed during the study period.

12.2.1. Duration of use

For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions were combined into continuous exposed episodes (drug eras). Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 7 days. Information on the duration of use of each of the antibiotics is available in the (https://data-dev.darwin-eu.org/EUPAS103381/).

The table below describes the median and P25-P75 of duration of use for those antibiotics belonging to the top 5 of most frequently prescribed antibiotics for at least one of the databases.

Table 12.2.1-1 Median [P25-P75] duration (in days) of use of antibiotics from the WHO Watch list –most prescribed drugs

Database name	CPRD GOLD	SIDIAP	IPCI	IQVIA Germany	IMASIS	CHUBX
	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)
Azithromycin	3 [1 - 3]	4 [4 - 4]	3 [3 - 3]	3 [3 - 3	1 [1 - 1]	3 [1 - 3]
Cefaclor	7 [5 - 7]	9 [8 - 9]	7 [6 - 7]	5 [1 – 7]	1 [1 - 1]	4 [2 - 4]
Ceftriaxone	7 [4 - 7]	5 [2 - 5]	30 [1 - 30]	7 [2 - 10	2 [1 - 2]	4 [2 - 4]
Cefuroxime	7 [7 - 7]	8 [6 - 8]	7 [7 - 7]	6 [6 - 7]	1 [1 - 1]	2 [1 - 2]
Ciprofloxacin	5 [5 - 5]	8 [8 - 8]	7 [7 - 7]	5 [5 - 10]	2 [1 - 2]	4 [2 - 4]
Clarithromycin	7 [7 - 7]	8 [8 - 8]	7 [7 - 7]	7 [5 - 7]	1 [1 - 1]	5 [3 - 5]
Erythromycin	7 [5 - 7]	9 [8 - 9]	7 [7 - 7]	30 [8 - 30]	1 [1 - 1]	4 [2 - 4]
Fosfomycin	1 [1 - 1]	3 [3 - 3]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
Levofloxacin	10 [7 - 10]	8 [8 - 8]	14 [7 - 14]	7 [5 - 10]	1 [1 - 1]	4 [1 - 4]
Lymecycline	56 [28 - 56]					4 [2 - 4]
Ofloxacin	14 [14 - 14]	11 [8 - 11]	14 [7 - 14]	30 [5 - 30]		4 [2 - 4]
Oxytetracycline	28 [7 - 28]	8 [4 - 8]	17 [12 - 17]	5 [5 - 7]	1 [1 - 1]	
Pheneticillin			7 [7 - 7]			
Piperacillin_tazobactam	28 [28 - 28]		37 [18 - 37]	30 [30 - 30]	6 [3 - 6]	6 [3 - 6]
Vancomycin	10 [10 - 10]	11 [6 - 11]	10 [7 - 10]	7 [5 - 10]	4 [2 - 4]	4 [2 - 4]

From this table, the median duration of use is shorter in hospital databases (IMASIS and CHUBX) compared to primary care databases which makes sense as antibiotic use in hospital databases mainly reflects inpatient care. In primary care databases, median duration of an antibiotic exposure period usually ranged around a week. In line with treatment recommendations on the use of fosfomycin, median duration was 1 day in all databases, except for 3 days in SIDIAP.

Drugs with a longer duration of use were lymecycline (CPRD GOLD – 56 days), erythromycin (IQVIA Germany – 30 days), ofloxacin (median duration ranging between 11-30 days in CPRD GOLD, SIDIAP, IPCI and IQVIA Germany), oxytetracycline in CPRD GOLD (28 days) and IPCI (17 days), piperacillin-tazobactam (28-37 days in CPRD GOLD, IPCI and IQVIA Germany)(but with low numbers) and vancomycin (around 10 days in CPRD GOLD, SIDIAP and IPCI).

12.2.2. Indication of use

Indication of use based on predefined infection cohorts

Next we estimated the indication of use (in terms of infection groups) for each incident prescribing of one of the antibiotics from the WHO Watch list. This information is available via the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/).

In this report, we focused on the indication of use for those drugs that were most frequently prescribed (top 5 of incidence rates per database) (see appendix – table 4). The indication of use was assessed in two time windows: 7 days before and after the index date and 30 days before to 7 days after the index date. This table is available in the appendix of the report. It is of notice that for all of the antibiotics, and for all of the databases, the proportion of prescriptions where either the indication is unknown (i.e. presence of a disease code but not belonging to any of the infection classes that has been generated) or the indication is missing (no disease code around the prescription) is high. For instance for ciprofloxacin, which is the antibiotic which belongs to the top 5 in all databases, the proportion where indication is unknown in time window [-7, 7] ranged between 29% in SIDIAP and 79% in CPRD GOLD (for [-30,7] 39% and 80% respectively). The proportion of prescriptions without indication ranged between 8% for CPRD GOLD and 47% for SIDIAP (for [-30,7] 3% and 33%). Similar findings were observed when exploring other antibiotics.

Also for fosfomycin which is an antibiotic mainly prescribed to treat urinary tract infections, the proportion of prescriptions with indication missing or unknown was high whereas the proportion of prescriptions with indication “Genitourinary tract infection” was less than 1% in all databases.

Indication of use for more severe infections (e.g. bone and joint infections, surgical site infections, infections of the central nervous system and catheter related infections) was more often recorded in secondary care databases (IMASIS and CHUBX) compared to primary care databases.

Top 10 of comorbidities, most frequently documented at time of antibiotic prescribing

All disease codes registered at the time of the index date (and in a sensitivity analysis in the 30 days prior to the index date) by antibiotic and by database, were identified and the top 10 – in terms of frequency – were generated This information is available for all the antibiotics from the WHO Watch list via the shiny app. (https://data-dev.darwin-eu.org/EUPAS103381/).

In the report, we again focused on those drugs most frequently prescribed (see appendix – table 5). Especially for antibiotics prescribed in primary care, the top 10 of disease codes often referred to infections. This is for instance demonstrated for fosfomycin where “urinary tract disease” was recorded at time of index date in

40% of the prescriptions. Similar for vancomycin, where disease codes in CPRD GOLD, IPCI, SIDIAP and IQVIA Germany referred to symptoms of diarrhea or clostridium difficile infections, which is the indication of use in primary care.

Disease codes as reported in secondare care data were less infection specific and often referred to symptomatology, lifestyle factors or comorbidities such as hypertension or hyperlipidemia.

12.2.5 Other Analysis

Results from sensitivity analyses (extending window to check for indication of use and top 10 of disease codes) and additional stratifications are available via the shiny app (https://data-dev.darwin-eu.org/EUPAS103381/.

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there was no requirement for expedited reporting of adverse drug reactions as mainly secondary data was used.

14 DISCUSSION

14.1 Key Results

Population level DUS

Although the list of antibiotics from the WHO Watch list is extensive (137 individual ingredients) only 78 of these were prescribed in at least one of the data sources during the study period. And of these antibiotics that were prescribed, few had an incidence rate > 100/100,000 PY (6 in CPRD GOLD, 9 in IPCI, 10 in SIDIAP, 12 in IMASIS, 7 in CHUBX and 14 in IQVIA Germany). Although the incidence rates varied between the primary care databases, those antibiotics with the highest incidence rates were the same within the databases with for instance high prescribing (amongst top 3) of ciprofloxacin in all 4 databases. Other drugs frequently prescribed in primary care were clarithromycin (CPRD GOLD and IPCI), fosfomycin (IPCI, SIDIAP and IQVIA Germany) and azithromycin (IPCI, SIDIAP and IQVIA Germany). As anticipated, the choice of antibiotic is different in secondary care with much higher use of ceftriaxone, vancomycin and meropenem .

Those antibiotics that belonged to the top 5 of prescribing amongst the different databases were further investigated to explore patterns over time. An increase in incidence rate over time was observed for ceftriaxone (IMASIS and CHUBX), cefuroxime (SIDIAP en IMASIS), piperacilline-tazobactam (CHUBX) and vancomycin (IMASIS). For azithromycin, different patterns were observed by database with an increase in IMASIS and SIDIAP up to 2018 and 2020 respectively, a decrease in IPCI and stable use in CPRD GOLD and CHUBX. A decrease or steady state in incidence rate was observed for the fluoroquinolones. Other antibiotics for which the incidence clearly decreased over time were pheneticillin (IPCI), oxytetracycline (CPRD GOLD), erythromycin (CPRD GOLD) and clarithromycin (CPRD GOLD).

Stratification of incidence rates by age group and sex was estimated for antibiotic class and not by individual antibiotic. In general, antibiotic use was lower in children than in adults and use increased with increasing age. For some of the antibiotics, use was also high in children or young adults such as macrolides, second generation cephalosporins and tetracyclines.

Use of antibiotics was comparable in males compared to females except for Beta lactamase-inhibitor_anti-pseudomonal antibiotics, carbapenem and 4th generation cephalosporins where use was higher in males than in females. For phosphonics, the opposite was observed with higher use in females.

The prevalence of antibiotic use very much mirrored the results of the incidence rates with highest use for azithromycin (especially in SIDIAP), ciprofloxacin, clarithromycin and fosfomycin.

Patient-level DUS

The median duration of antibiotic use was shorter in hospital databases (IMASIS and CHUBX) compared to primary care databases. This shorter duration may be related to the fact that inpatient exposure is short as patients are usually discharged within days following hospital admission. In primary care databases, the median duration of an antibiotic exposure period ranged around a week except for fosfomycin where median duration was around 1 day. Shorter median duration for inpatient use can also be explained by the fact that some of these antibiotics were prescribed for surgical profylaxis (which usually is for less than 24 hours).

With regard to the indication of use, the proportion of prescriptions where either the indication is unknown (i.e. presence of a disease code but not belonging to any of the infection classes that has been generated) or the indication is missing (no disease code around the prescription) is high.

The top 10 of disease codes reported at the time of the prescription date (i.e. index date), proved to be informative as these conditions often referred to infections (some of which were not yet included amongst the concept codes to define the different types of infections).

14.2 Limitations of the research methods

General limitations:

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

Drug prescriptions: A recording of a prescription did not mean that the patient took the drug. Therefore, assumptions of actual use and the duration of drug use were made.

Indication: The actual reason for prescription of the drug was not recorded as such in the databases. We assessed indication via a proxy based on a recording of pre-defined conditions recorded around the date of therapy initiation. Therefore, recording of potential indication might be incomplete. In addition, the recording of events used for patient characterisation varied across databases. Categories of infections were defined based on the SNOMED dictionary. However, from this report, not all infections fell under these categories.

Setting: For this study, we included data from 2 hospital data sources (CHUBX in France and IMASIS in Spain). Results of these databases may not necessarily reflect antibiotic prescription, dispensation and/or administration in other hospital databases.

14.3 Results in context

Although the list of antibiotics from the WHO Watch list is large, prescribing was limited to 78 antibiotics based on whether these drugs were registered in the countries of interest (countries of the respective databases) and national guidelines with regard to appropriate antibiotic prescribing.

For some of the antibiotics, an increase was observed over time especially for those drugs mainly administered in secondary care (ceftriaxone, cefuroxime (both primary and secondary care), piperacilline-

tazobactam and vancomycin) whereas the other antibiotics remained stable over time or decreased. A study published in 2018, on global antibiotic consumption also reported stable rates of antibiotic prescribing between 2010-2015 in high income countries. (16) The surveillance report from the ECDC on antimicrobial consumption in the EU also reported an increase in use of third generation cephalosporins, glycopeptides and piperacillin+enzyme inhibitor in the hospital setting in the period between 2010-2019 which is in line with our findings. (17)

14.4 Generalisability

This study included data from 6 different European countries and healthcare systems (primary care in IPCI, SIDIAP, IQVIA Germany and CPRD GOLD and secondary care in IMASIS and CHUBX). While we consider results largely representative for the general population needing treatment with antibiotics, results should not be generalised to the whole of Europe as difference in type of antibiotics by country were observed. Antibiotics prescribing very much relates to national guidelines on the appropriate use of antibiotics in the primary and secondary care setting. Still, it is likely to assume that trends with regard to changes over time, effect of age and sex but also indication of use and duration of prescriptions are comparable amongst other European countries.

14.5 Other information

NA

15 CONCLUSION

Of the list of antibiotics from the WHO Watch list (137 individual ingredients), exposure to any of these drugs was reported for 78 antibiotics of this list. Incidence rate were mainly below 100/100.000 PY except for use of ciprofloxacin, clarithromycin, fosfomycin and azithromycin in most of the database. The incidence rate remained stable or decreased over time except for ceftriaxone, cefuroxime, piperacilline-tazobactam and vancomycin that were mainly prescribed in secondary care. For the majority of investigated antibiotics, the incidence increased with age and was comparable by sex. The median duration of use was usually around one week but shorter in secondary care.

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17 ANNEXES

Appendix I: List of Stand-Alone documents

TABLE 1: LIST WITH CONCEPT DEFINITIONS FOR INDICATION OF USE

Indication of use	Concept ID Included	Concept ID Excluded
Cardiovascular System Infection	4028265	42537043, 42537216, 4119591, 4193175, 42537495, 4103844, 4207188
Bloodstream infection	132736, 132797, 4331670,	42537043, 42537216, 42537495, 45757222
Catheter-related Infection	42537043, 42537216, 42537495	
Central Nervous System Infection	4028070	4027382, 4237782, 4266366, 374278, 381783
Gastrointestinal System Infection	37396146	4112288, 4341228, 3655333, 37116438, 37017318, 4207191, 36716496, 42537647, 4345693, 196620, 4340791, 36717503, 4340113, 37110318, 36716876, 196347, 4341225
Pneumonia	255848	4049965, 4050872, 261326
Lower Respiratory Tract Infection other than pneumonia	256451, 4270490	4278083, 4058712
Bone and Joint Infection	4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 72410	4157481, 37017284, 4343916, 80184
Eye, Ear, Nose, Throat or Mouth Infection	4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613	4208666, 4085100, 4122211, 4149910, 4122756, 37396756, 4208812, 4220916
Genitourinary Tract Infection	4193167	
Skin and Soft Tissue Infection	4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028,	4290719, 42536747, 37017777, 37396839, 4341774, 4342877, 3655664, 3655670, 3655330,

Indication of use	Concept ID Included	Concept ID Excluded
	4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222, 4316194, 4048751, 4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281	4030291, 3655666, 3655610, 607399
Surgical Site Infection	437474	
Other Infection	432250	4028265, 132736, 4331670, 42537043, 42537216, 42537495, 4028070, 37396146, 255848, 256451, 4270490, 4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613, 4193167, 4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986,

Indication of use	Concept ID Included	Concept ID Excluded
		4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222, 4316194, 4048751, 4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281, 437474, 432251, 440029, 763528, 3654645, 3655580, 3655670, 4030507, 4080879, 4105474, 4188426, 4193174, 4193987, 4208780, 4249564, 4249828, 4270602, 4345236, 4345692, 36715551, 36715566, 36717290, 37017777, 37394534, 37394535, 37394536, 42536622

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

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

TABLE 2: LISTS WITH CONCEPT DEFINITIONS FOR EXPOSURE

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

Antibiotic	Class	ATC code	ConceptID
Arbekacin	Aminoglycosides	J01GB12	21603005
Aspoxicillin	Penicillins	J01CA19	40255264
Azithromycin	Macrolides	J01FA10	21602978

Antibiotic	Class	ATC code	ConceptID
Azlocillin	Penicillins	J01CA09	21602828
Bekanamycin	Aminoglycosides	J01GB13	40255908
Biapenem	Carbapenems	J01DH05	21602924
Carbenicillin	Penicillins	J01CA03	21602822
Carindacillin	Penicillins	J01CA05	21602824
Cefaclor	Second-generation cephalosporins	J01DC04	21602886
Cefamandole	Second-generation cephalosporins	J01DC03	21602885
Cefbuperazone	Second-generation cephalosporins	J01DC13	40255561
Cefcapene-pivoxil	Third-generation cephalosporins	J01DD17	21602911
Cefdinir	Third-generation cephalosporins	J01DD15	21602909
Cefditoren-pivoxil	Third-generation cephalosporins	J01DD16	21602910
Cefepime	Fourth-generation cephalosporins	J01DE01	21602915
Cefetamet-pivoxil	Third-generation cephalosporins	J01DD10	21602904
Cefixime	Third-generation cephalosporins	J01DD08	21602902
Cefmenoxime	Third-generation cephalosporins	J01DD05	21602899
Cefmetazole	Second-generation cephalosporins	J01DC09	21602891
Cefminox	Second-generation cephalosporins	J01DC12	40255560
Cefodizime	Third-generation cephalosporins	J01DD09	21602903
Cefonicid	Second-generation cephalosporins	J01DC06	21602888
Cefoperazone	Third-generation cephalosporins	J01DD12	21602906
Ceforanide	Second-generation cephalosporins	J01DC11	21602893
Cefoselis	Fourth-generation cephalosporins	to be assigned	2000000002
Cefotaxime	Third-generation cephalosporins	J01DD01	21602895
Cefotetan	Second-generation cephalosporins	J01DC05	21602887
Cefotiam	Second-generation cephalosporins	J01DC07	21602889
Cefoxitin	Second-generation cephalosporins	J01DC01	21602883
Cefozopran	Fourth-generation cephalosporins	J01DE03	21602917

Antibiotic	Class	ATC code	ConceptID
Cefpiramide	Third-generation cephalosporins	J01DD11	21602905
Cefpirome	Fourth-generation cephalosporins	J01DE02	21602916
Cefpodoxime-proxetil	Third-generation cephalosporins	J01DD13	21602907
Cefprozil	Second-generation cephalosporins	J01DC10	21602892
Cefsulodin	Third-generation cephalosporins	J01DD03	21602897
Ceftazidime	Third-generation cephalosporins	J01DD02	21602896
Cefteram-pivoxil	Third-generation cephalosporins	J01DD18	715906
Ceftibuten	Third-generation cephalosporins	J01DD14	21602908
Ceftizoxime	Third-generation cephalosporins	J01DD07	
Ceftriaxone	Third-generation cephalosporins	J01DD04	21602898
Cefuroxime	Second-generation cephalosporins	J01DC02	21602884
Chlortetracycline	Tetracyclines	J01AA03	21602801
Cinoxacin	Quinolones	J01MB06	21603033
Ciprofloxacin	Fluoroquinolones	J01MA02	21603009
Clarithromycin	Macrolides	J01FA09	21602977
Clofoctol	Phenol derivatives	J01XX03	21603063
Clomocycline	Tetracyclines	J01AA11	21602809
Delafloxacin	Fluoroquinolones	J01MA23	715911
Demeclocycline	Tetracyclines	J01AA01	21602799
Dibekacin	Aminoglycosides	J01GB09	21603002
Dirithromycin	Macrolides	J01FA13	21602981
Doripenem	Carbapenems	J01DH04	21602923
Enoxacin	Fluoroquinolones	J01MA04	21603011
Ertapenem	Carbapenems	J01DH03	21602922
Erythromycin	Macrolides	J01FA01	21602970
Fidaxomicin	Macrolides	A07AA12	43534745
Fleroxacin	Fluoroquinolones	J01MA08	21603015
Flomoxef	Second-generation cephalosporins	J01DC14	40255562

Antibiotic	Class	ATC code	ConceptID
Flumequine	Quinolones	J01MB07	21603034
Flurithromycin	Macrolides	J01FA14	21602982
Fosfomycin_oral	Phosphonics	J01XX01	21603061
Fusidic-acid	Steroid antibacterials	J01XC01	21603052
Garenoxacin	Fluoroquinolones	J01MA19	21603026
Gatifloxacin	Fluoroquinolones	J01MA16	21603023
Gemifloxacin	Fluoroquinolones	J01MA15	21603022
Grepafloxacin	Fluoroquinolones	J01MA11	21603018
Imipenem/cilastatin	Carbapenems	J01DH51	21602925
Isepamicin	Aminoglycosides	J01GB11	21603004
Josamycin	Macrolides	J01FA07	21602975
Kanamycin_IV	Aminoglycosides	J01GB04	21600610
Kanamycin_oral	Aminoglycosides	A07AA08	21602997
Lascufloxacin	Fluoroquinolones	J01MA25	947811
Latamoxef	Third-generation cephalosporins	J01DD06	21602900
Levofloxacin	Fluoroquinolones	J01MA12	21603019
Levonadifloxacin	Fluoroquinolones	J01MA24	947889
Lincomycin	Lincosamides	J01FF02	21602986
Lomefloxacin	Fluoroquinolones	J01MA07	21603014
Loracarbef	Second-generation cephalosporins	J01DC08	21602890
Lymecycline	Tetracyclines	J01AA04	21602802
Meropenem	Carbapenems	J01DH02	21602921
Metacycline	Tetracyclines	J01AA05	21602803
Mezlocillin	Penicillins	J01CA10	21602829
Micronomicin	Aminoglycosides	to be assigned	2000000001
Midecamycin	Macrolides	J01FA03	21602972
Minocycline_oral	Tetracyclines	J01AA08	21602806

Antibiotic	Class	ATC code	ConceptID
Miocamycin	Macrolides	J01FA11	21602979
Moxifloxacin	Fluoroquinolones	J01MA14	21603021
Nemonoxacin	Quinolones	J01MB08	1588669
Neomycin_IV	Aminoglycosides	J01GB05	21602998
Neomycin_oral	Aminoglycosides	A07AA01	21600603
Netilmicin	Aminoglycosides	J01GB07	21603000
Norfloxacin	Fluoroquinolones	J01MA06	21603013
Ofloxacin	Fluoroquinolones	J01MA01	21603008
Oleandomycin	Macrolides	J01FA05	21602973
Oxolinic-acid	Quinolones	J01MB05	21603032
Oxytetracycline	Tetracyclines	J01AA06	21602804
Panipenem	Carbapenems	J01DH55	21602926
Pazufloxacin	Fluoroquinolones	J01MA18	21603025
Pefloxacin	Fluoroquinolones	J01MA03	21603010
Penimepicycline	Tetracyclines	J01AA10	21602808
Pheneticillin	Penicillins	J01CE05	21602845
Pipemidic-acid	Quinolones	J01MB04	21603031
Piperacillin	Penicillins	J01CA12	21602866
Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05	21602831
Piromidic-acid	Quinolones	J01MB03	21603030
Pristinamycin	Streptogramins	J01FG01	21602988
Prulifloxacin	Fluoroquinolones	J01MA17	21603024
Ribostamycin	Aminoglycosides	J01GB10	21603003
Rifabutin	Rifamycins	J04AB04	21603099
Rifampicin	Rifamycins	J04AB02	21603097
Rifamycin_IV	Rifamycins	J04AB03	21603098
Rifamycin_oral	Rifamycins	A07AA13	715872

Antibiotic	Class	ATC code	ConceptID
Rifaximin	Rifamycins	A07AA11	21600613
Rokitamycin	Macrolides	J01FA12	21602980
Rolitetracycline	Tetracyclines	J01AA09	21602807
Rosoxacin	Quinolones	J01MB01	21603028
Roxithromycin	Macrolides	J01FA06	21602974
Rufloxacin	Fluoroquinolones	J01MA10	21603017
Sarecycline	Tetracyclines	J01AA14	715904
Sisomicin	Aminoglycosides	J01GB08	21603001
Sitafloxacin	Fluoroquinolones	J01MA21	40256175
Solithromycin	Macrolides	J01FA16	1123620
Sparfloxacin	Fluoroquinolones	J01MA09	21603016
Spiramycin	Macrolides	J01FA02	21602971
Streptoduocin	Aminoglycosides	J01GA02	21602993
Streptomycin_IV	Aminoglycosides	J01GA01	21600606
Streptomycin_oral	Aminoglycosides	A07AA04	21602992
Sulbenicillin	Penicillins	J01CA16	21602835
Tazobactam	Beta-lactamase-inhibitors	J01CG02	21602860
Tebipenem	Carbapenems	J01DH06	715908
Teicoplanin	Glycopeptides	J01XA02	21603044
Telithromycin	Macrolides	J01FA15	21602983
Temafloxacin	Fluoroquinolones	J01MA05	21603012
Temocillin	Penicillins	J01CA17	21602836
Ticarcillin	Penicillins	J01CA13	21602832
Tobramycin	Aminoglycosides	J01GB01	21602995
Tosufloxacin	Fluoroquinolones	J01MA22	715910
Troleandomycin	Macrolides	J01FA08	21602976
Trovafloxacin	Fluoroquinolones	J01MA13	21603020
Vancomycin_IV	Glycopeptides	J01XA01	21600611

Antibiotic	Class	ATC code	ConceptID
Vancomycin_oral	Glycopeptides	A07AA09	21603043