

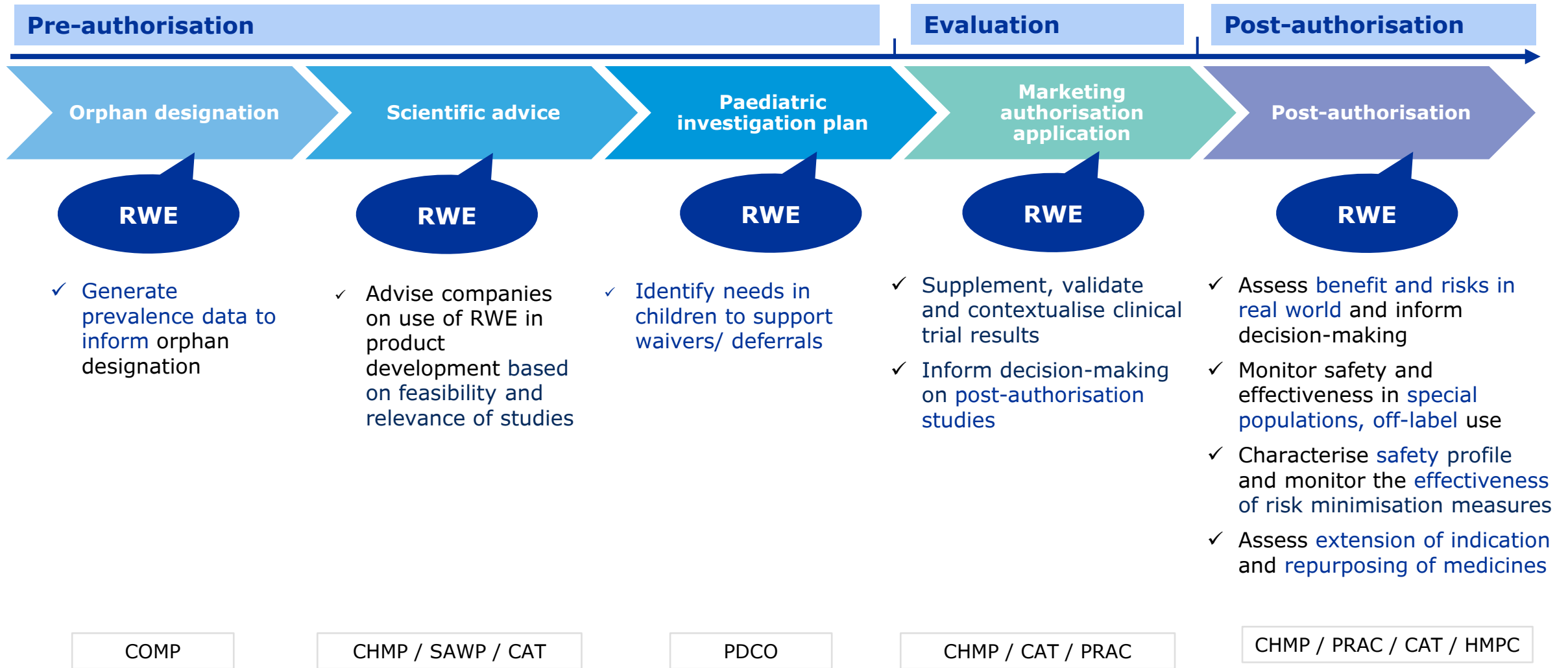
Real World Evidence update

21st Industry Stakeholder Platform – Operation of EU Pharmacovigilance

20 October 2026

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RWE use across the medicinal product lifecycle



The Netherlands

Integrated Primary Care Information
Netherlands Cancer Registry

Belgium

IQVIA Longitudinal Patient Database Belgium
UZA Antwerpen
Belgian Cancer Registry

United Kingdom

UK BioBank
Clinical Practice Research Datalink GOLD
Clinical Practice Research Datalink AURUM
National Neonatal Research Database

France

Bordeaux University Hospital
Système National des Données de Santé
Health Data Warehouse of Assistance Publique
French National Registry of Rare Diseases

Germany

IQVIA Disease Analyzer Germany
InGef Research Database
Dresden University Hospital

Portugal

ULSM-RT
Egas Moniz Health Alliance DataBase
IPO Porto

Spain

SIDIAP
BIFAP
IMASIS and IMIM
Valencia Health System Integrated Database
H120
Health Data Research Platform of the Balearic Islands
Hospital Universitario Virgen Macarena

Norway

Norwegian Linked Health Registry
Cancer Registry of Norway

Sweden

Health Impact

Finland

FinOMOP

Estonia

Estonian Biobank

Lithuania

Lithuanian Health Data

Denmark

Danish Health Data Registries

Poland

Children's Memorial Health
Institute Database

Hungary

Semmelweis University Clinical Data

Croatia

National Public Health Information System

Greece

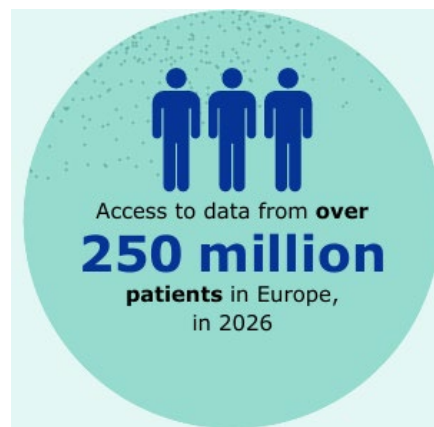
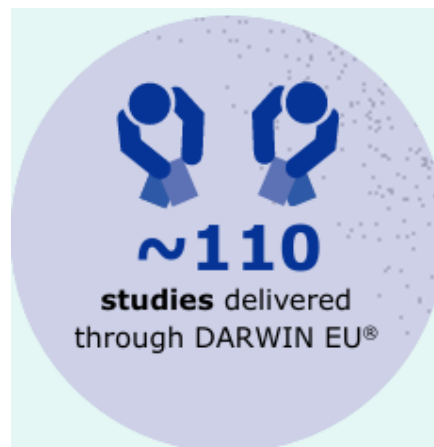
Papageorgiou General Hospital

Italy

POLIMI
Pedianet

United States of America

IQVIA US Ambulatory EMR, PharMetrics, Oncology



Feb 2025 – Feb 2026 RWE analyses

108

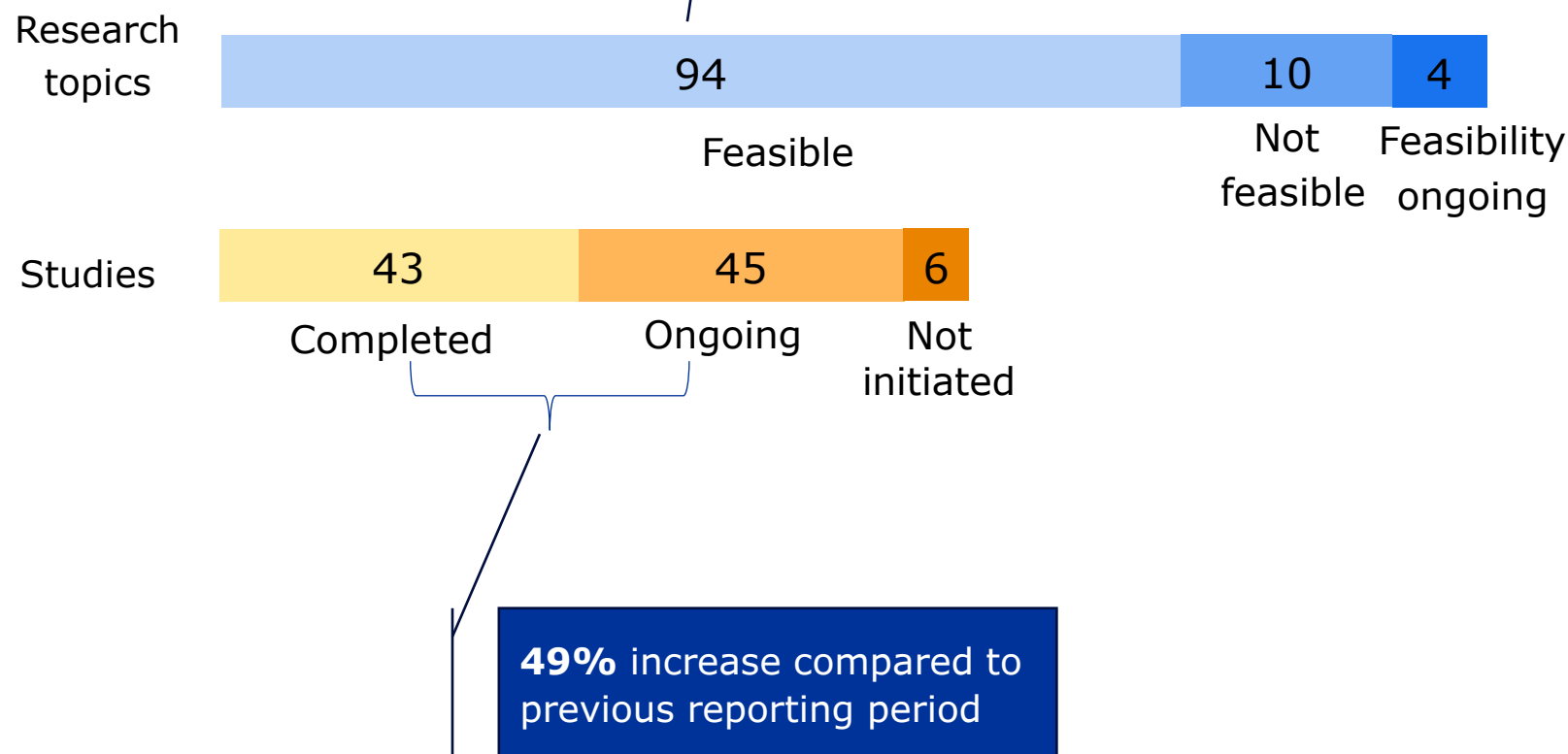
Research topics
(Feb '25 – Feb '26)

92

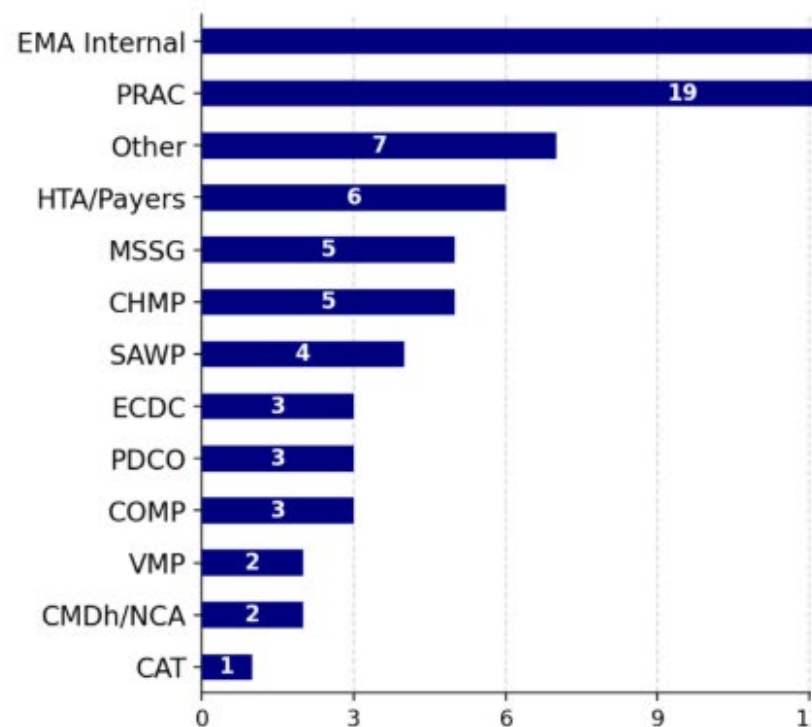
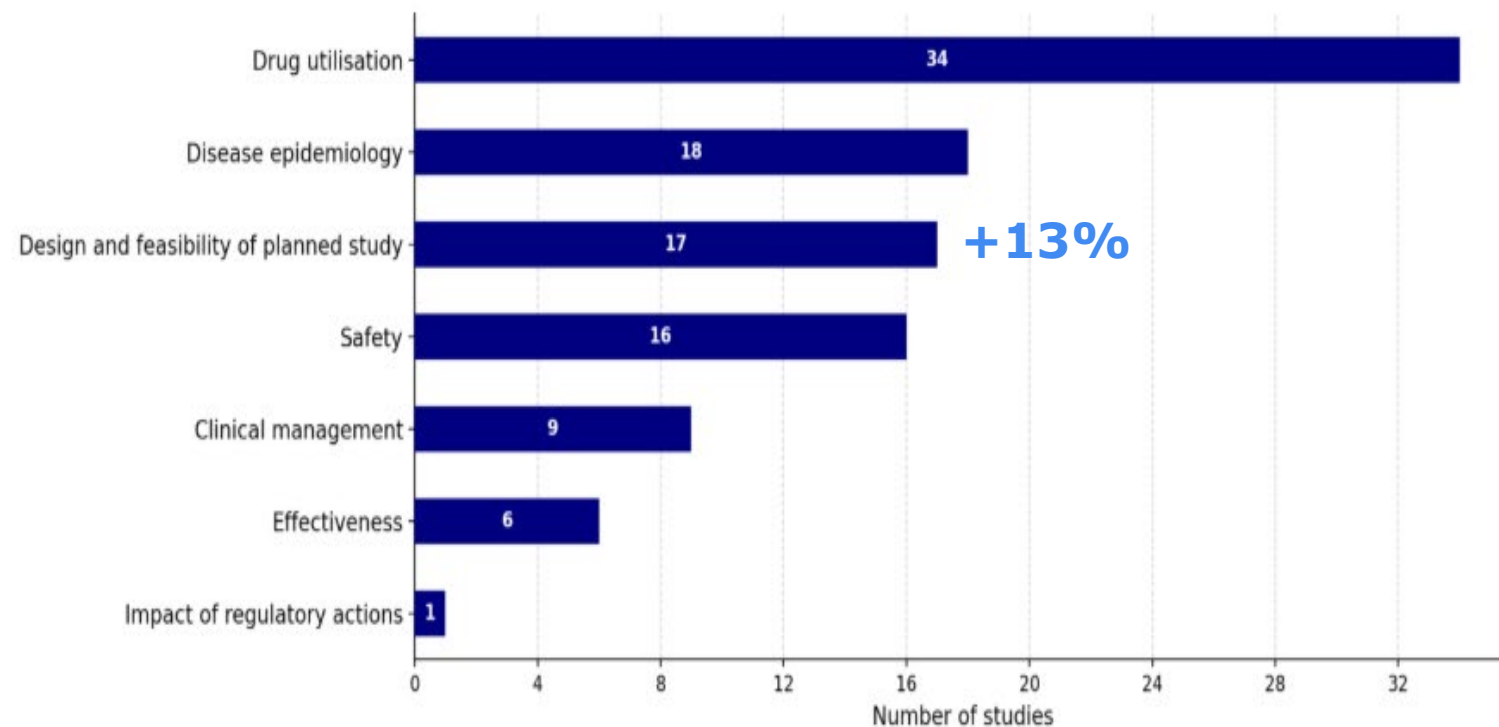
DARWIN EU

15

FWC



Main requesters of RWE



Selected use cases

Risk of suicidality after taking the antibiotic doxycycline

PRAC

Need for the study

Doxycycline is a **broad-spectrum antibiotic**, widely used to treat bacterial infections. It can be used for **treatment of moderate or severe acne**.

Based on spontaneous case reports, recent concerns have been raised about its side effects, particularly suicidality, but the data have been limited.

How was the study conducted?

The study generated more information to understand if the medicine is linked to suicidality. It looked at people who started taking doxycycline and compared their risk to people taking other medicines for treating acne or infections. It also considered the different health conditions the medicine is used to treat.

Data from 3 European countries were analysed.

How were the results used?

The study **helped PRAC assess whether doxycycline might be linked to suicidal thoughts or behaviour**. The committee concluded that the current evidence is not sufficient to establish a causal relationship between doxycycline and the risk of suicidality.

A separate DARWIN EU study showed the **risk of suicidality is higher in patients with skin disorders, including acne**.

Why this matters?

The study helped alleviate safety concerns and reassured patients using the medicine. This is important as the medicine is commonly used to treat acne, urinary tract and respiratory infections.

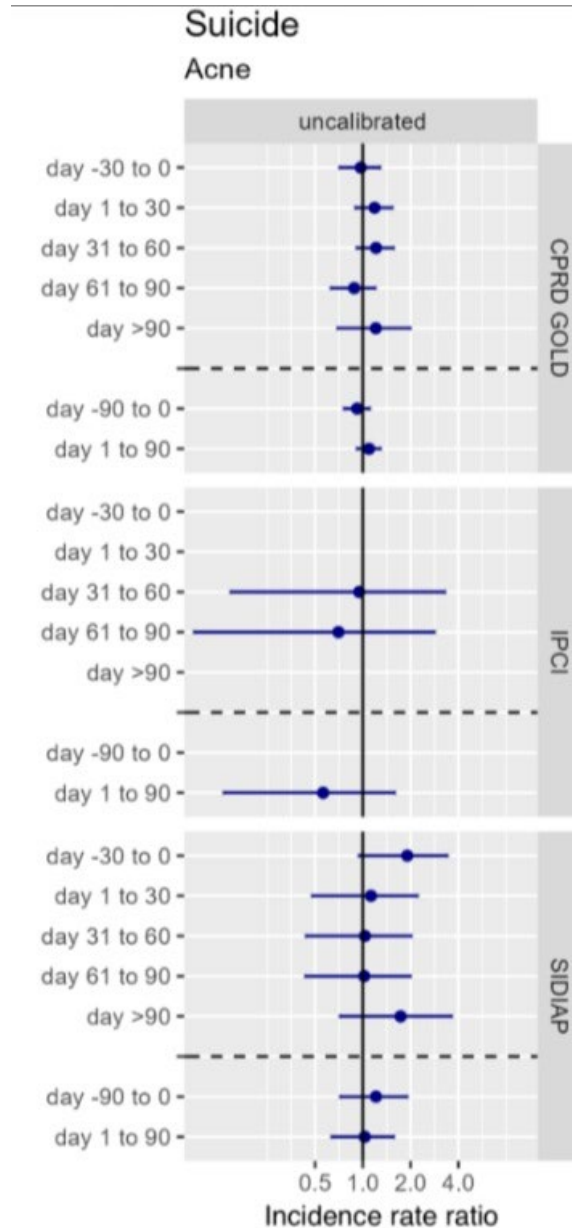
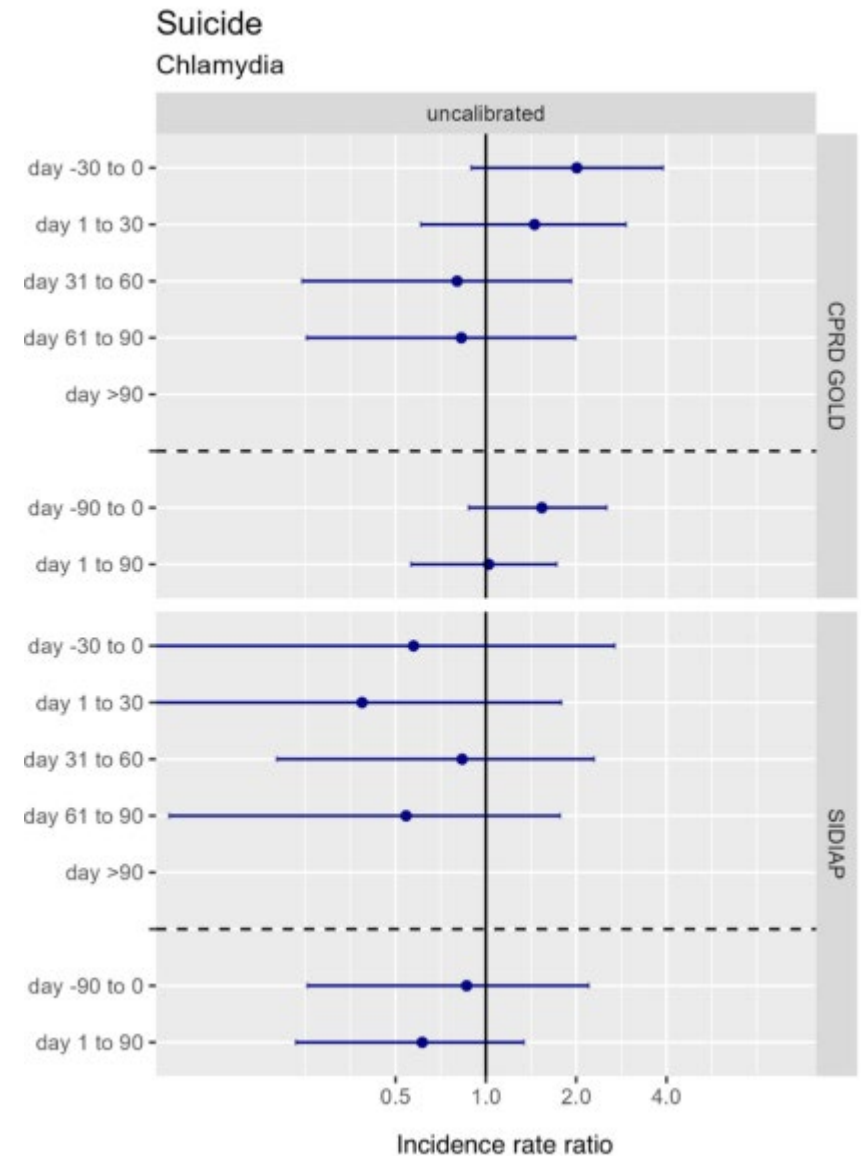
2 analytical approaches:

1. New user cohort with active comparators

chosen per indication (not shown) – risk differences per indication are likely

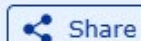
2. Self-controlled case series

where each user serves as their own control – comparing risk in risk windows during/before/after use (results shown)
➔ Better control for fixed confounders





Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 25-28 November 2024



Share

Doxycycline: currently available evidence not supporting link with risk of suicidality

EMA's safety committee ([PRAC](#)) has concluded that the currently available evidence is not sufficient to establish a causal relationship between the use of the antibiotic doxycycline and the risk of suicidality.

Doxycycline is a broad-spectrum antibiotic, widely used to treat a wide range of infections caused by bacteria such as acne, urinary and lower respiratory tract infections, dental infections, and skin infections. It is also used to prevent the development of certain infections, such as malaria.

A [safety signal](#) on the risk of suicidality, suicidal thoughts or actions with doxycycline was raised based on cases reported to the Finnish [national competent authority](#), as well as further cases reported to [EudraVigilance](#), the centralised European database of suspected side effects reports, and the medical literature.

The [PRAC](#) started its review in November 2023 and requested the [marketing authorisation holders](#) for doxycycline to perform a cumulative review of the data from all relevant sources.

The [PRAC](#) also requested a study based on real-world evidence, which includes data from electronic health records and disease registries, through [DARWIN EU](#)  to facilitate the assessment of the signal. After reviewing all available evidence from spontaneous reports, the literature, the discussion on possible mechanisms and the study performed via DARWIN EU, the [PRAC](#) considered that the evidence is not sufficient to establish a causal relationship and that no update to the [product information](#) of doxycycline is warranted.

Suicide-related events in relation to doxycycline will be closely monitored and any new evidence will be discussed in the Periodic Safety Update Reports (PSURs).

DARWIN EU® - Clozapine and the risk of agranulocytosis - updated risk-minimisation measures

- This study investigated the **incidence, timing of agranulocytosis and neutropenia** in new users of clozapine, a medication used for treatment-resistant schizophrenia and Parkinson's disease associated psychosis.
- Despite its effectiveness, clozapine may be underused due to the risk of severe blood-related side effects and the burden of long-term monitoring to prevent the side-effects.
- The study included over 40,000 patients from five European databases – DK, FI, DE, HR, ES
- The incidence of agranulocytosis and neutropenia was very low across all data sources, with most events occurring within the first two months of treatment. The risk remained low throughout the follow-up period, and there were no significant differences by age or sex.
- PRAC used the results to update its **recommendations for clozapine monitoring, including less frequent blood count monitoring** and focusing solely on the **absolute neutrophil count** (ANC), which were shown by the current evidence to be more specific and the most relevant marker for the risk of neutropenia.

Table 11. Proportion of individuals diagnosed with agranulocytosis or neutropenia (broad definition) among new users of clozapine during the study period, per data source.

	Number of individuals	Number of events
DK-DHR	4,207	<5
FinOMOP-HILMO	14,942	66
IQVIA DA Germany	4,008	6
NAJS	13,368	6
SIDIAP	4,346	36

- In FinOMOP-HILMO, the weekly incidence rate peaked at 58.7 per 1,000 PY during the ninth week after clozapine initiation, followed by a decline. Subsequently, many intervals either showed no events or had a low event count.
- In SIDIAP, incidence rates were low and relatively stable across the follow-up period with either zero or a low event count (<5), except for a peak of 18.7 per 1,000) PY in the second month.

Table 17. Treatment duration of clozapine prescriptions, presented by database.

		DK-DHR	FinOMOP-HILMO	IQVIA DA Germany	NAJS	SIDIAP
		(n = 4,253)	(n= 14,944)	(n = 4,029)	(n = 13,382)	(n = 4,348)
days exposed*	Mean (SD)	315.17 (702.21)	262.06 (559.02)	266.19 (404.42)	164.19 (315.29)	843.97 (964.67)
	Median (Q25 - Q75)	66 (8 - 236)	53 (30 - 201)	100 (50 - 300)	42 (30 - 145)	428 (154 - 1,166)
	Min	1	2	1	1	1
	Max	5,398	4,299	4,295	2,705	4,929

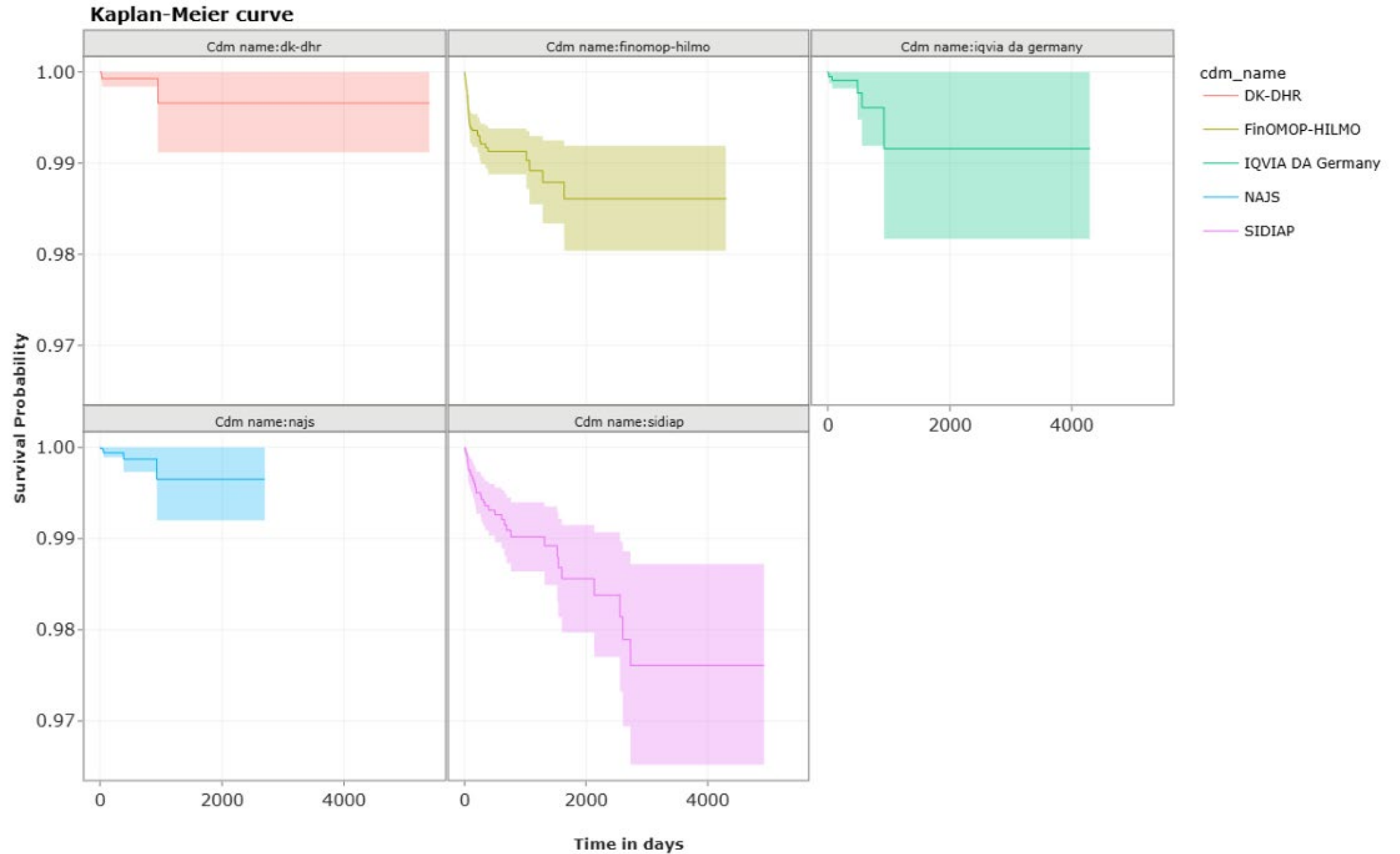


Figure 4. Kaplan-Meier plots of time to agranulocytosis or neutropenia (broad definition) following clozapine treatment initiation by data source.



Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7 – 10 July 2025

11 July 2025

Ixchiq: temporary restriction on vaccinating people 65 years and older to be lifted

News

Human

Pharmacovigilance

New safety information for healthcare professionals

Clozapine: Revised recommendations for routine blood count monitoring

PRAC has endorsed a DHPC informing about revised recommendations for the monitoring of the blood count to minimise the risk of severe neutropenia and agranulocytosis with clozapine.

Clozapine is an atypical antipsychotic medicine indicated in treatment-resistant schizophrenia patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including other atypical antipsychotics. It is also used in psychotic disorders occurring during Parkinson's disease, in cases where standard treatment has failed.

Clozapine is known to increase the risk for neutropenia and agranulocytosis, and regular blood count monitoring is in place to minimise this risk. Neutropenia involves low levels of a type of white blood cells called neutrophils, which can leave patients vulnerable to infections. Agranulocytosis involves a sudden and sharp decrease of neutrophils, representing a very serious form of neutropenia.

New evidence from the scientific literature suggests that, although clozapine-induced neutropenia can occur at any time during treatment, it is predominantly observed during the first year, with the incidence peaking in the first 18 weeks of treatment. After this the incidence decreases becoming progressively lower after two years of treatment in patients without previous episode of neutropenia.

Therefore, PRAC recommended less frequent blood count monitoring. For example, in patients without neutropenia, the frequency of monitoring is reduced to every 12 weeks after one year, and to once a year after two years of treatment. Furthermore, monitoring is now recommended to be based solely on the count of absolute neutrophil count (ANC), a measure of the number of neutrophils. This aligns with current evidence that ANC is a more specific and clinically relevant marker for assessing the risk of neutropenia. Therefore, the requirement for monitoring white blood cell counts has been removed.

The product information for all clozapine-containing medicines will be updated to reflect the monitoring frequency for the risk of clozapine-related agranulocytosis and the revised ANC thresholds for treatment initiation and continuation.

The DHPC for clozapine will be disseminated to healthcare professionals by the marketing authorisation holders, according to an agreed communication plan, and published on the [Direct healthcare professional communications](#) page and in [national registers](#) in EU Member States.

Next – GLP1RA DUS:
Overall use of GLP1RAs is increasing
(hot off the press: study report to be published soon)

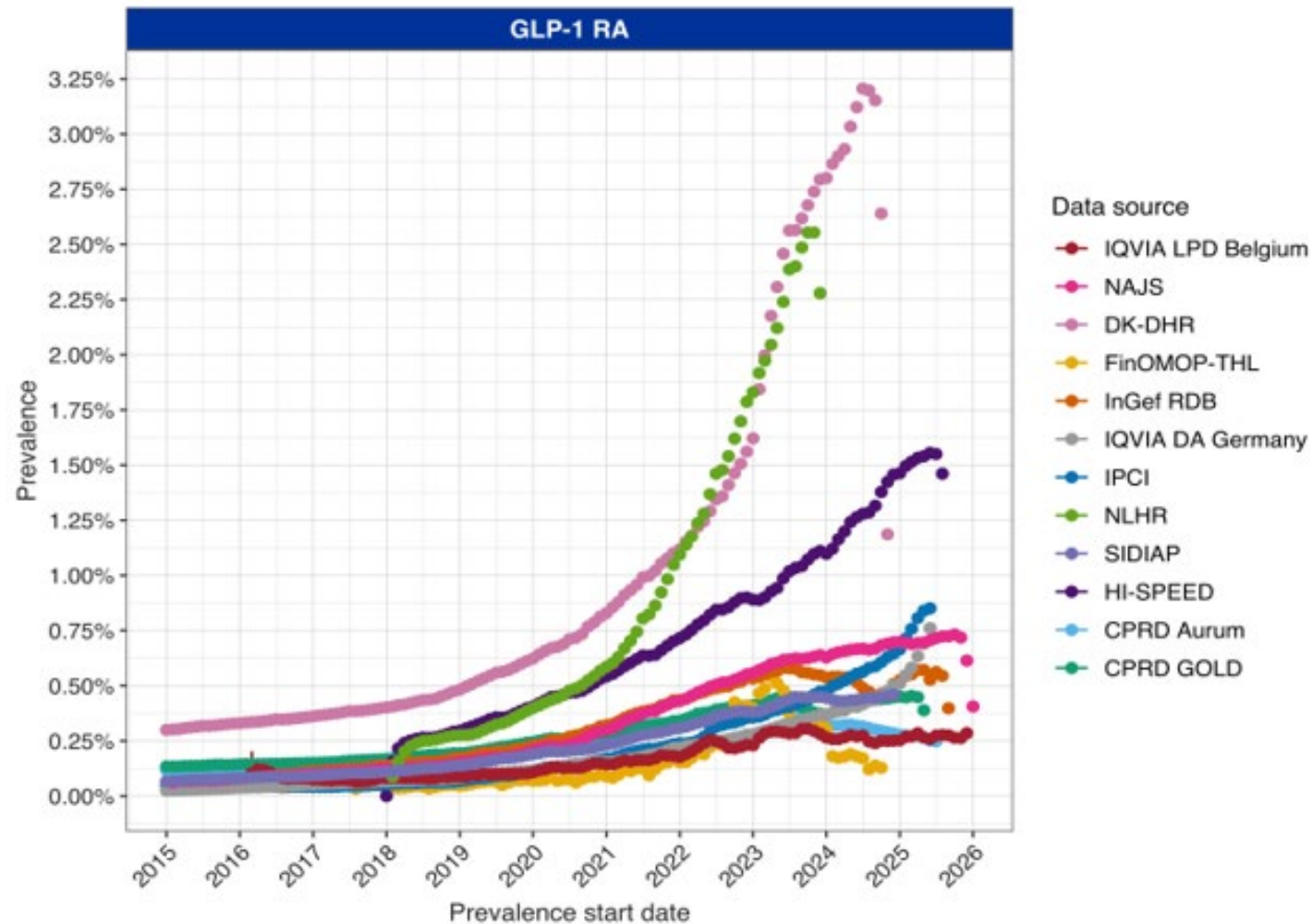


Figure 33. Prevalence of GLP-1 RA class per data source.

Classified as public by the European Medicines Agency

Burden of ADRs of GLP1 RAs (Hot off the press, report under review)

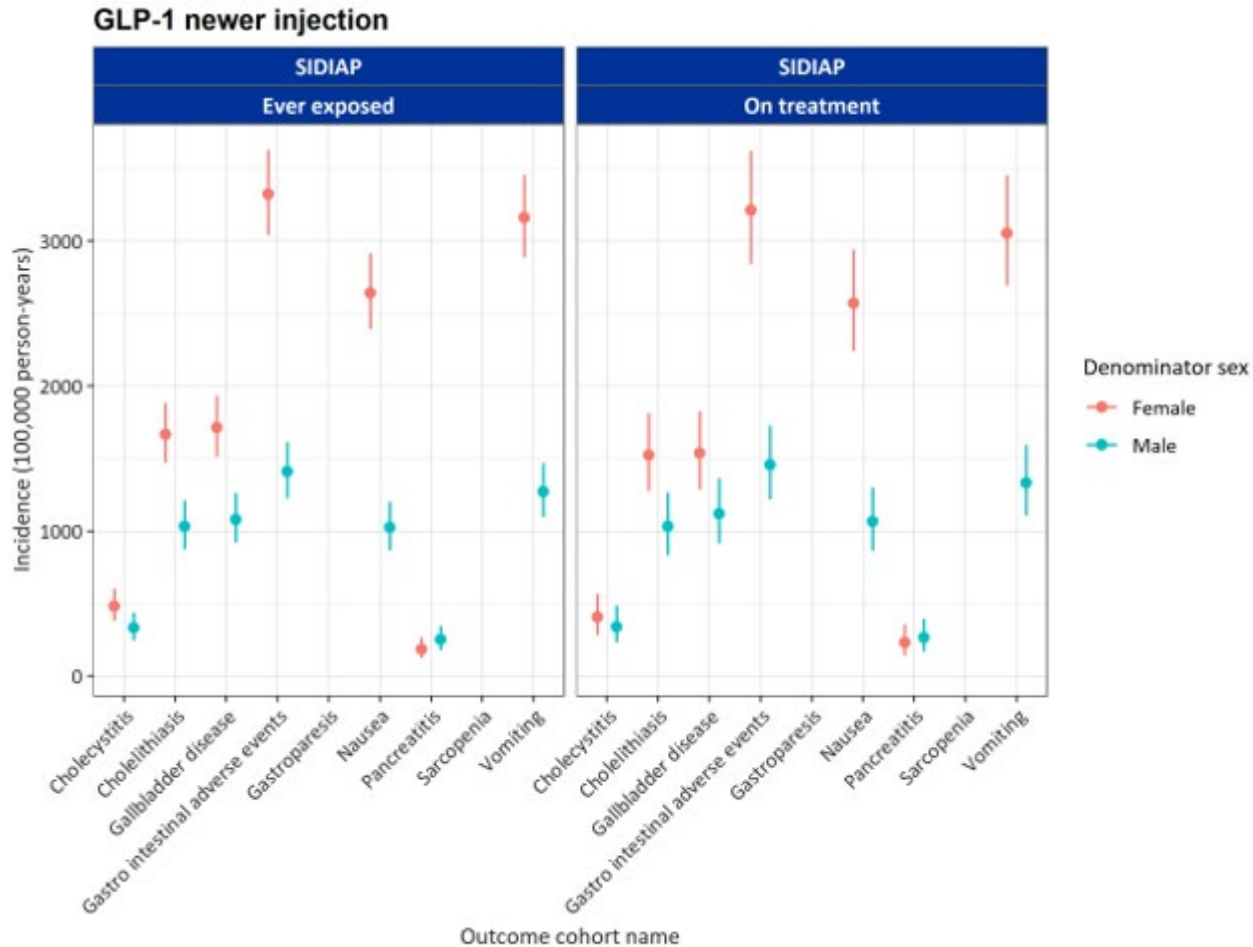


Figure 42. Incidence rate among GLP-1 newer injection cohort in SIDIAP.

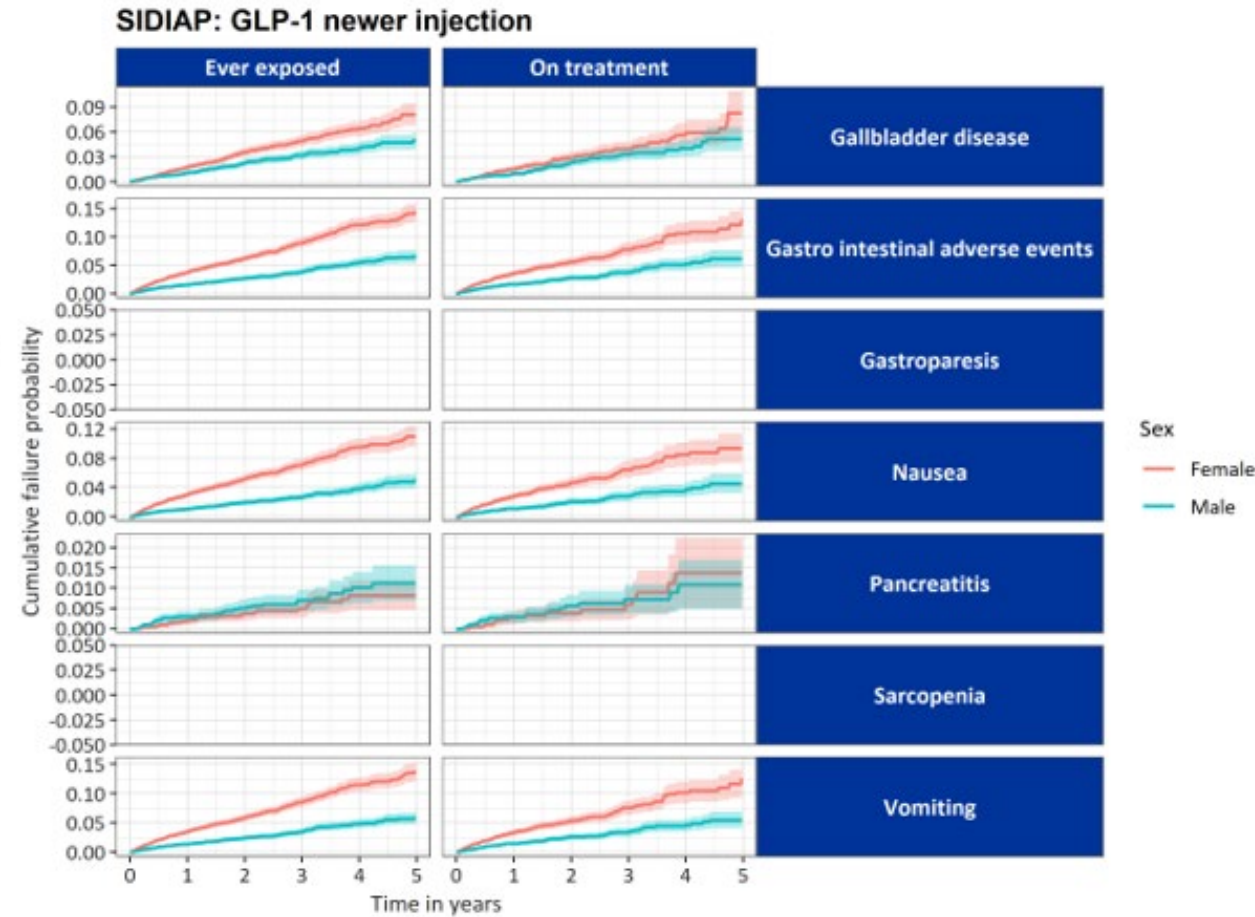


Figure 43. Cumulative incidence among GLP-1 newer injection in SIDIAP.

On-going program of studies focusing on women's health

- 1) Sex differences in treatment patterns for primary hypertension and venous thromboembolic events in European countries
- 2) Approaches to identifying drug exposure during pregnancy
- 3) Incidence of cancer among pregnant women
- 4) Number of pregnancies among women using statins or with clear indication for statin treatment
- 5) **Sex-specific incidence of selected adverse events in users of GLP1 receptor agonists, SGLT2 inhibitors and HMG CoA reductase inhibitors (statins)**
- 6) Diagnosis, treatment and impact of endometriosis over time
- 7) Diagnosis, treatment, and health impact of polyendocrine metabolic ovarian syndrome
- 8) Sex differences in benzodiazepine use of adolescents/young adults

DARWIN E non-steroid years using

First published: 16/01/20

EU PAS number: EUPAS1

Study

Finalised

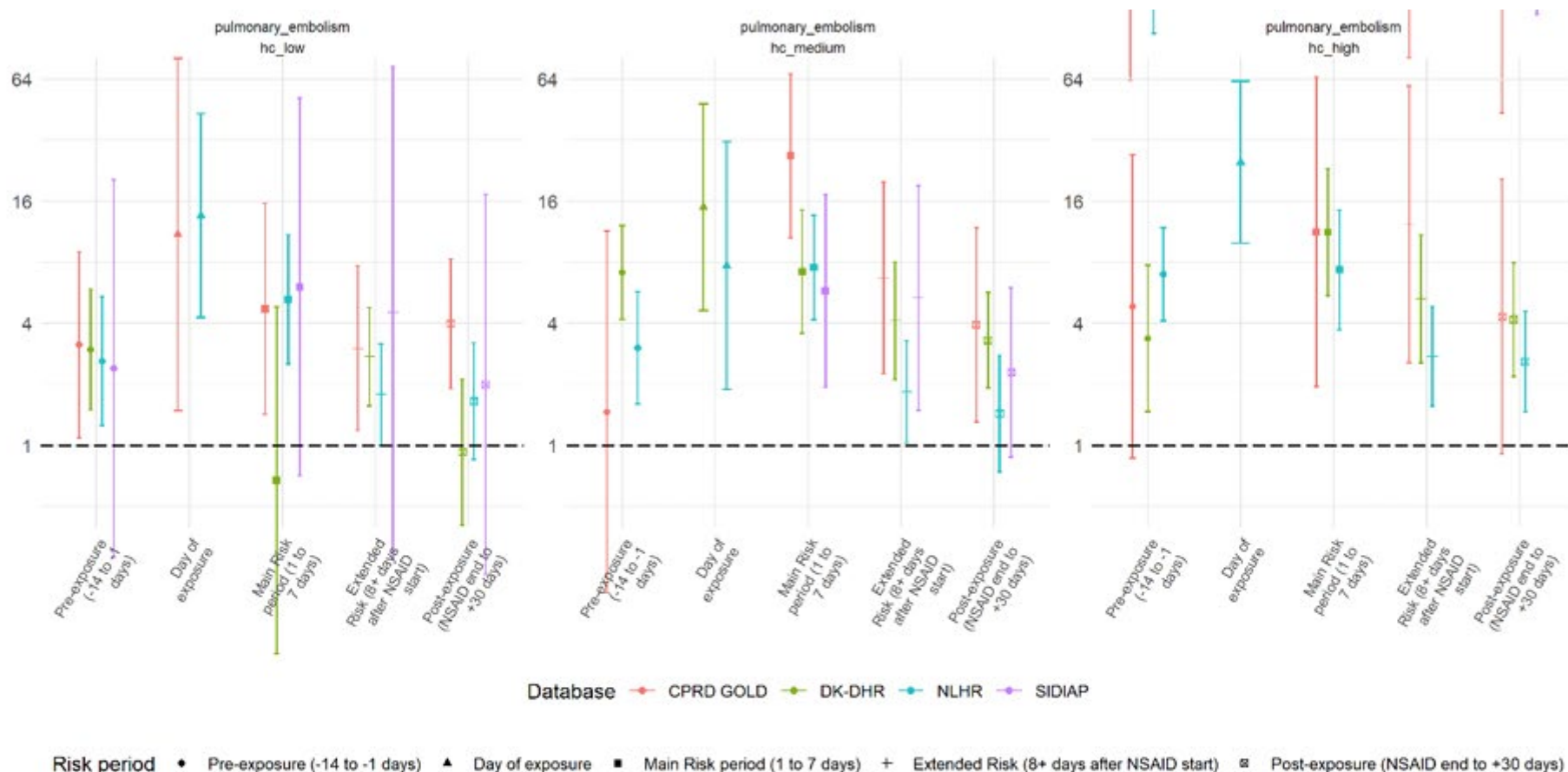


Figure 6. Adjusted incidence rate ratio (IRR) of VTE, pulmonary embolism, and deep vein thrombosis during each pre-defined period of any NSAIDs use. X-axis present the pre-exposure, day of exposure, main risk period, extended risk period, and post-exposure periods. Y-axis present the adjusted incidence rate ratio of each period. Rows: outcome of VTE, deep vein thrombosis, and pulmonary embolism. Columns: Low-,

Overall survival in patients with non-small cell lung cancer treated with selected immunotherapies as first treatment

*HTA
bodies
and
payers*

Need for the study

Health technology assessment (HTA) bodies and payers requested the study in pursuit of evidence to better understand the **effectiveness of immunotherapies compared to chemotherapies** used to treat **non-small cell lung cancer (NSCLC)** in real-world settings.

This pilot study helped EMA understand evidence gaps by HTA bodies/payers and how to generate RWE for them.

How was the study conducted?

A comparative study to assess the **overall survival of patients with locally advanced or metastatic NSCLC who start treatment with immunotherapies** and how it compares to the survival of patients who get chemotherapies as first treatment.

The study used **data from 3 EU countries (FR, ES, NL), including NL cancer registry** data.

How were the results used?

The results show that people with NSCLC tend to live longer when treated with immunotherapy, (particularly the most used pembrolizumab), compared to chemotherapy when used as first treatment.

This was after considering other factors that affect survival, such as age, sex, year of starting the treatment, tumour stage and patients' general wellbeing.

Why this matters

The first oncology study by DARWIN EU provides valuable insights into the effectiveness of immunotherapies versus chemotherapies in a real-world setting.

Better understanding of lung cancer treatments is important because these therapies are expensive and increasingly used as the population ages and more people are diagnosed with lung cancer.

Results

Estimated overall survival by treatment in Netherlands Cancer Registry

Treatment	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	● 5,425	4,134	9.96 (9.56, 10.41)	17.25 (16.79, 17.71)	44.06 (42.72, 45.44)	27.04 (25.82, 28.33)	20.19 (19.04, 21.40)
Pembrolizumab	● 7,992	4,906	13.11 (12.58, 13.63)	20.14 (19.71, 20.60)	52.15 (51.01, 53.32)	34.77 (33.59, 35.99)	26.95 (25.74, 28.22)
Nivolumab	213	147	12.19 (9.43, 14.59)	16.92 (14.49, 19.32)	50.00 (43.26, 57.81)	25.04 (19.07, 32.89)	17.56 (12.26, 25.16)
Nivolumab + ipilimumab	62	27	16.16 (11.53, 35.74)	20.86 (15.21, 26.55)	62.04 (48.20, 79.86)	28.50 (15.63, 51.96)	22.80 (10.84, 47.95)

Comparison of overall survival of patients with locally advanced or metastatic NSCLC under pembrolizumab to that of exclusive chemotherapy as first-line treatment in NCR after propensity score matching

Cohort	Treatment	Patients (n)	Events (n)	Hazard Ratio	95% CI
Target	Pembrolizumab	3,003	1,966	0.66	0.62-0.70
Comparator	Chemotherapy	3,003	2,332	1.00	--

Propensity score matching was conducting including the following covariates: **age, sex, index year, stage of tumour, and WHO performance status (WHO-PS).**

Take home messages:

- RWE is routinely being used across medicines lifecycle in EU: DUS, disease epi, safety + effectiveness studies
- Standardised analytics used in federated DARWIN EU network allow rapid study conduct when required
- Data granularity and power can be an issue for rare exposures/outcomes





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Thank you

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Backup slides

Use of higher-risk antibiotics from the WHO Watch list, including azithromycin

CHMP

Need for the study

The antibiotic **azithromycin** has been used for decades to treat various infections in children and adults. It is [listed by the WHO](#) as an essential medicine.

The medicine is also classified in the [WHO's Watch category](#) due to its **higher risk of antimicrobial resistance** (AMR). Data show that resistance against this antibiotic has increased in recent years.

How was the study conducted?

Commissioned by EMA, the [study](#) looked at how the **141 antibiotics on the WHO's 'Watch' list**, including azithromycin, are prescribed and for how long.

The study used data from routine clinical care in **5 European countries**.

The results show a **broad use of azithromycin** across Europe, both in adults and children, with the medicine ranking among the top 5 to 10 in most databases.

How were the results used?

The study provided data on the use of the antibiotic across Europe.

CHMP used the results when it **re-evaluated the benefits and risks of azithromycin** medicines given by mouth or infusion (drip) into a vein. The aim was to promote a more rational medicine use to preserve its effectiveness.

The results help track the use of antibiotics that need to be closely monitored due to potential risks – like fluoroquinolones.

Why this matters?

Based on its assessment, CHMP recommended several changes to the way azithromycin is used in the EU, including the removal of certain indications.

Using this common antibiotic more wisely will help the EU monitor antibiotic use and support global fight against AMR.

Updated data has just been received

- Working with ECDC, the ATB DUS was repeated
- covering **all WHO (2023) AWaRe antibiotics** per classification lists Access, Watch, Reserve
- includes 258 antibiotics and data from 11 countries

→ Incidence

→ User characteristics

→ Indication for use incl. changes over time

The [study report](#) is published.

- Azithromycin

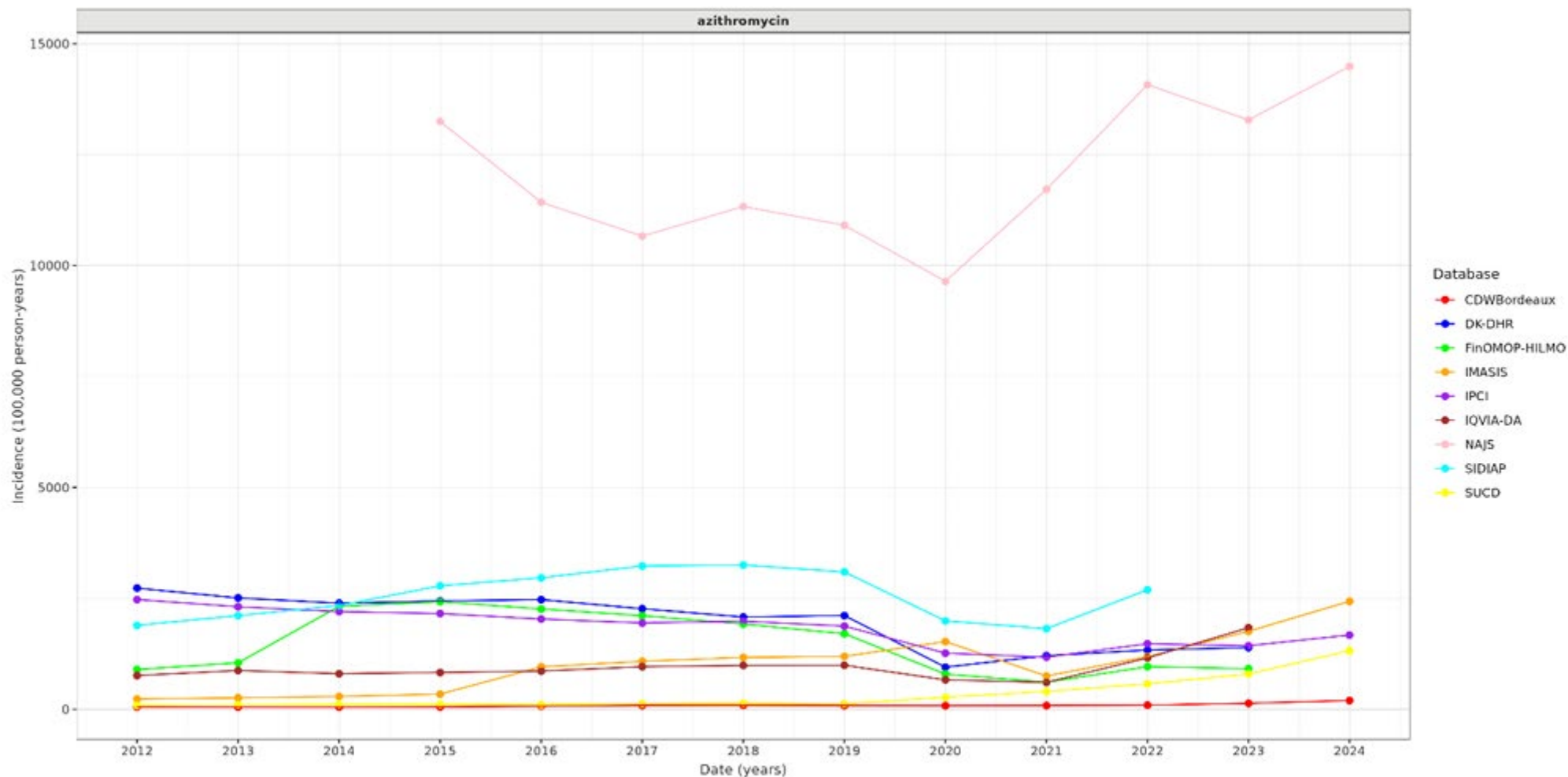


Figure 181. Overall yearly incidence rates per 100,000 PYs of azithromycin antibiotic in data sources NAJS, DK-DHR, FinOMOP-THL, CDW Bordeaux, IQVIA DA Germany, SUCD, IPCI, IMASIS, SIDIAP over years 2012–2024.

- Amoxicillin

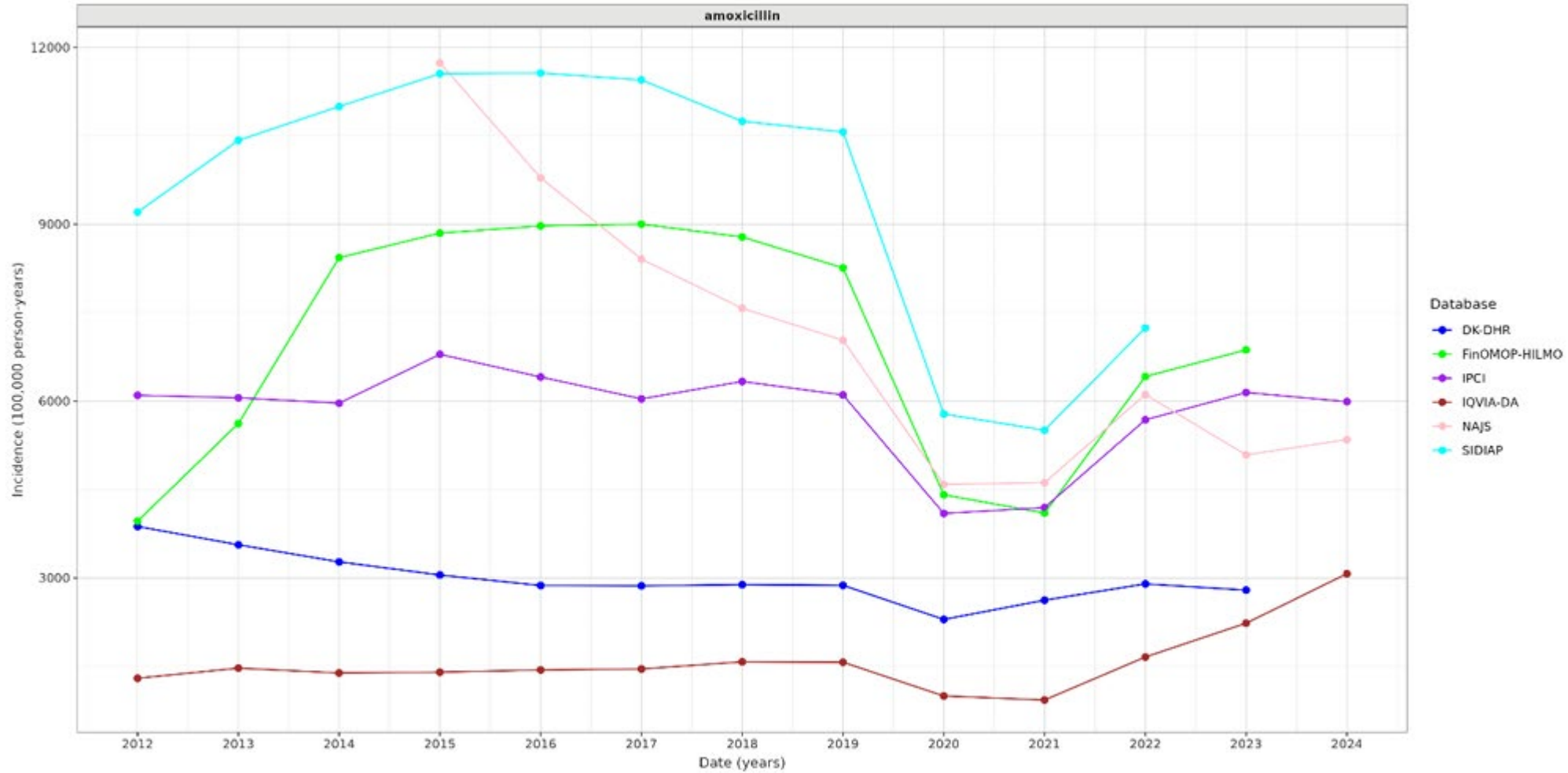


Figure 18. Yearly incidence rates per 100,000 PYs of amoxicillin antibiotic in data sources NAJS, DK-DHR, FinOMOP-THL, IQVIA DA Germany, IPCI, SIDIAP over years 2012–2024.

- Doxycycline

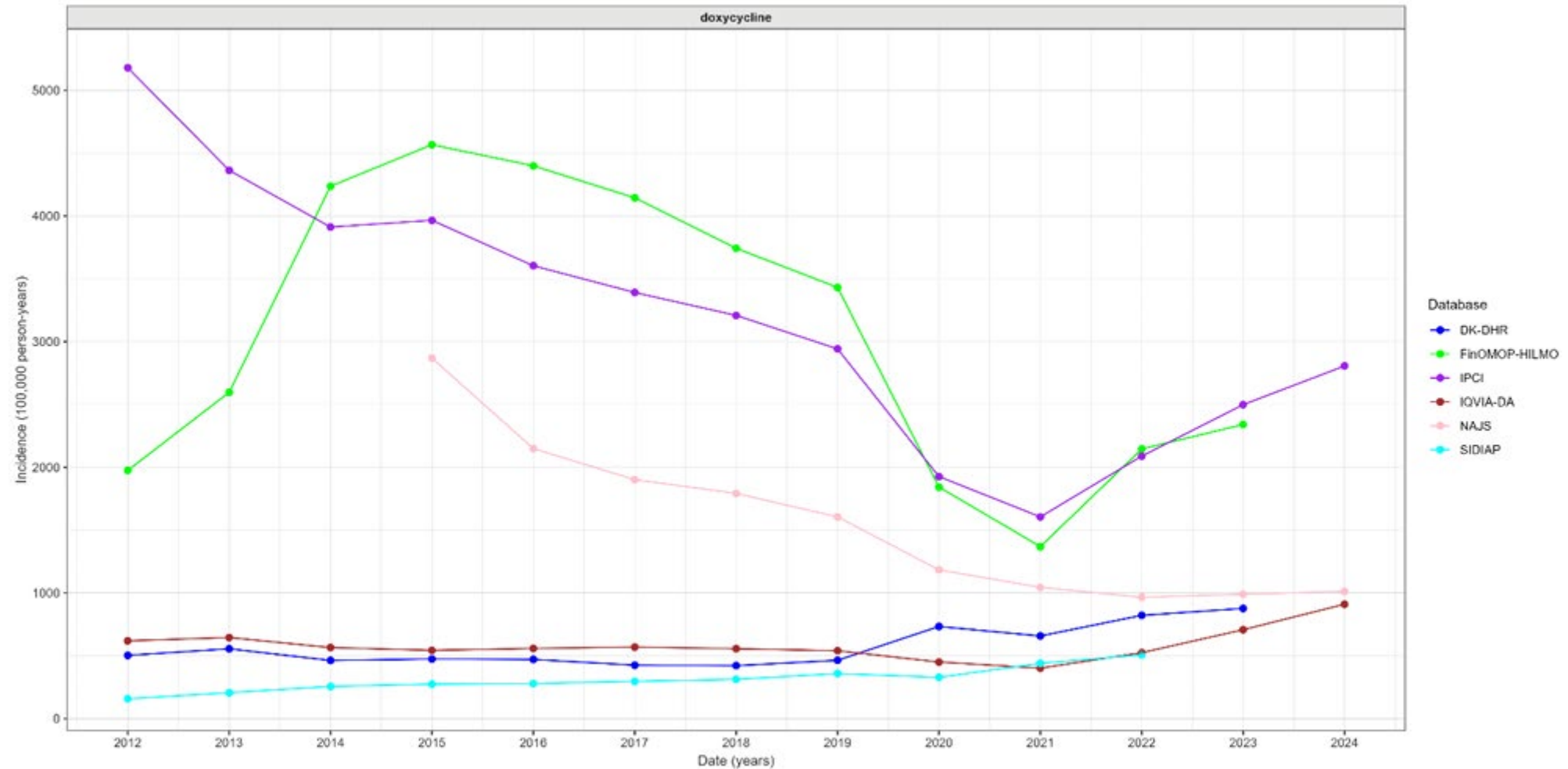


Figure 25. Yearly incidence rates per 100,000 PYs of Doxycycline antibiotic in data sources NAJS, DK-DHR, FinOMOP-THL, IQVIA DA Germany, IPCI, SIDIAP over years 2012–2024.

- Doxycycline



Figure 153. Temporal trends in the indication of use for doxycycline antibiotics from the WHO AWaRe 'Access' category at the index date.

- Doxycycline

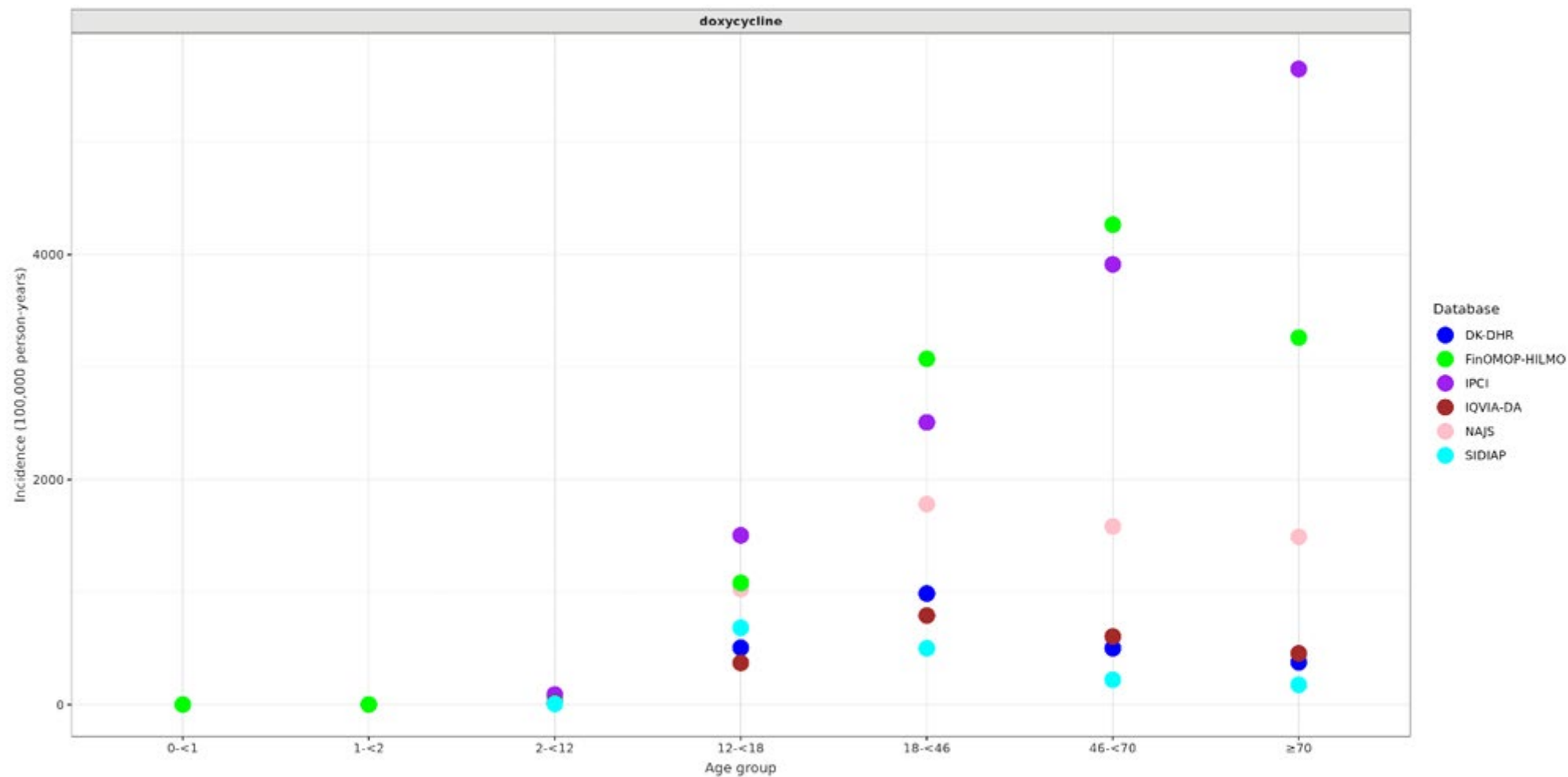


Figure 121. Incidence rates per 100,000 PYs of doxycycline antibiotic in data sources NAJS, DK-DHR, FinOMOP-THL, IQVIA DA Germany, IPCI, SIDIAP stratified by age categories, 2012–2024.