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EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Changes in use and utilisation patterns of drugs with reported shortages between 2010 and 2024 in Europe and North America: a network cohort study

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'The MegaStudy' → 52 databases included

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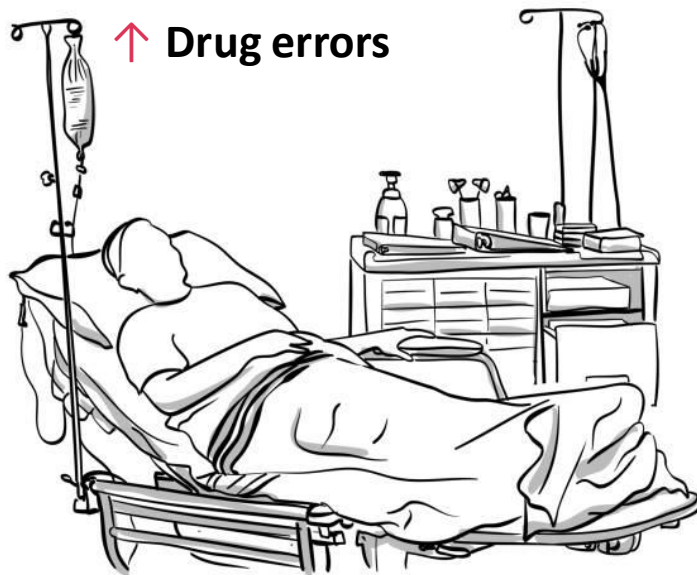
This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (grant number 806968).



BACKGROUND



↑ Mortality
↑ Adverse events
↑ Drug errors



Exacerbated during COVID-19 outbreak

During lockdown²:

- Reduction or cessation of local/global transportations
- Supply chain disruption (including drugs production and distribution)

COVID-19 vaccines as an example³:

- High demand, insufficient to cover the worldwide
- Unequal distribution

¹ Phuong, J.M., et al., *The impacts of medication shortages on patient outcomes: A scoping review*. PLoS One, 2019. 14(5): p. e0215837.

² Ayati, N., P. Saiyarsarai, and S. Nikfar, *Short and long term impacts of COVID-19 on the pharmaceutical sector*. Daru, 2020. 28(2): p. 799-805.

³ Klobucista, C. *A Guide to Global COVID-19 Vaccine Efforts*. 2022 [cited 2023]. Available from: <https://www.cfr.org/backgrounder/guide-global-covid-19-vaccine-efforts>.



AIMS OF THE STUDY

1. To describe the incidence and prevalence of medicines with (suggested) shortages over time, and their alternatives

Population-level drug utilisation study

*-> incidence and prevalence of drugs stratified
by calendar year, age, sex and healthcare settings*

IncidencePrevalence

CRAN 0.7.4 codecov unknown R CMD-check passing
Lifecycle Experimental

Package overview

IncidencePrevalence contains functions for estimating population-level incidence and prevalence using the OMOP common data model. For more information on the package please see our paper in *Pharmacoepidemiology and Drug Safety*.

Raventós, B, Català, M, Du, M, et al. IncidencePrevalence: An R package to calculate population-level incidence rates and prevalence using the OMOP common data model. *Pharmacoepidemiol Drug Saf*. 2023; 1-11. doi: 10.1002/pds.5717



Study period: 2010-2024





AIMS OF THE STUDY

2. To characterise incident and prevalent users receiving a medicine with (suggested) shortages and their alternatives

Patient-level drug utilisation study

*-> characterisation of drug users stratified by calendar year,
including drug use: information on potential indication,
treatment duration, and dosage*

DrugUtilisation



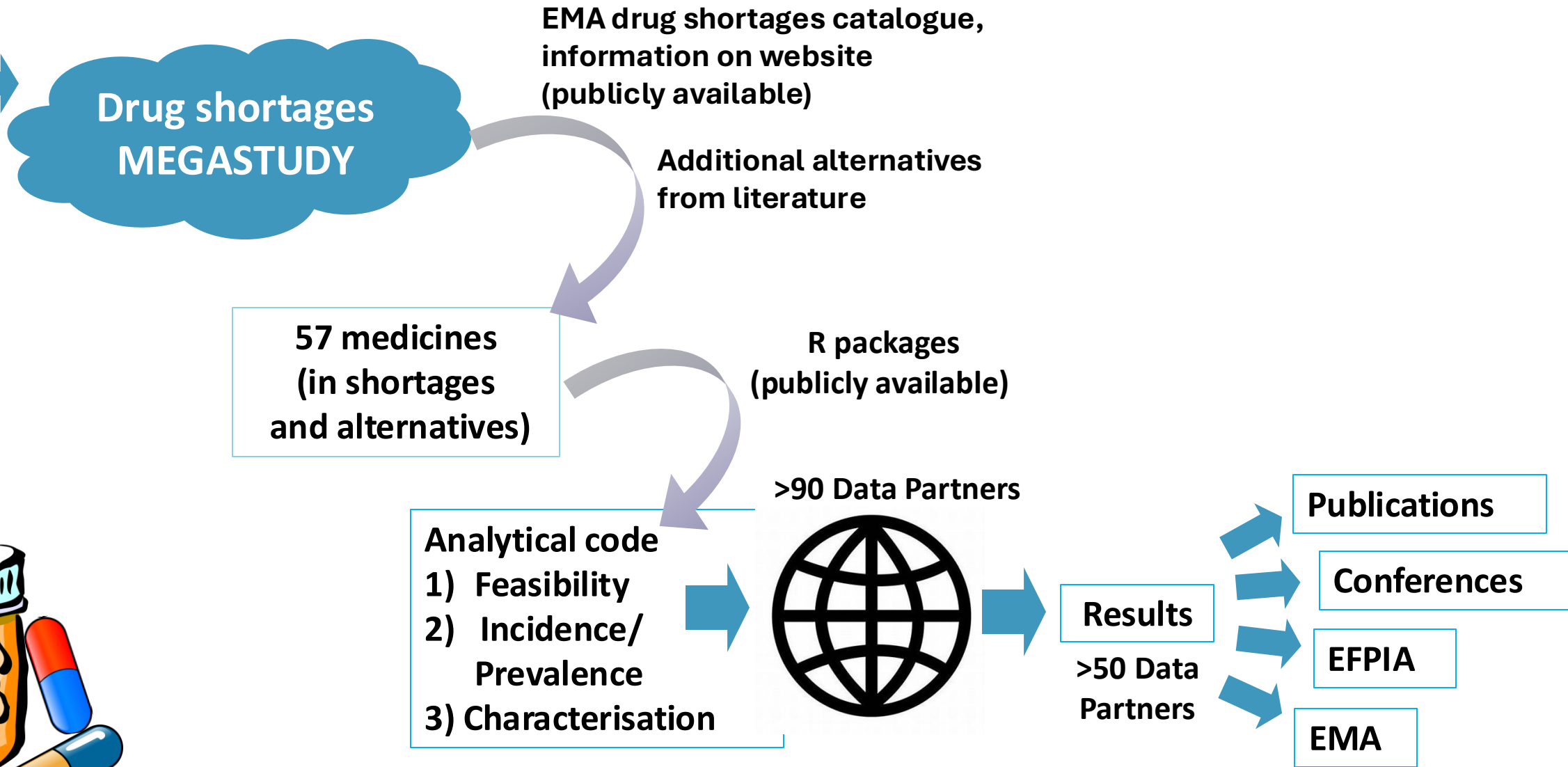
CRAN 0.7.1 codecov 82% R-CMD-check passing Lifecycle Experimental

Package overview

DrugUtilisation contains functions to instantiate and characterise drug cohorts in data mapped to the OMOP Common Data Model. The package supports:

Study period: 2010-2024







MEDICINES OF INTEREST (EMA CATALOGUE CUT-OFF DATE 25.09.23)

Drugs with shortage (n=16)	Shortage start date	Shortage end date
Alteplase, Tenecteplase	23/09/2022	28/08/2024
Sarilumab	09/11/2021	14/09/2023
Verteporfin	08/11/2021	Ongoing shortage
Varenicline	08/07/2021	Ongoing shortage
C1 esterase inhibitor	29/06/2017 06/08/2018	06/11/2017 25/06/2020
Arsenic trioxide	31/07/2017	06/09/2018
Belatacept	17/03/2017	29/09/2023
Ganirelix	16/02/2017	08/11/2022
Imiglucerase	04/11/2013	01/10/2018
Agalsidase_beta	04/11/2013	07/06/2016
Tigecycline	22/05/2015	07/11/2019
Amoxicillin +/- clavulanate	27/01/2023	Ongoing shortage
Ceftozolane-tazobactam	22/12/2020	14/04/2023

+ 41 alternatives



52 DATABASES INCLUDED

Num	Database acronym	Database name - full	Total N Database	Earliest date	Latest date	Data type	Country
1	ULSRA	Unidade Local de Saúde da Região de Aveiro	514,014	2010-01-01	2023-12-31	secondary	Portugal
2	ULSEDV	Unidade Local de Saúde de Entre Douro e Vouga	562,687	2010-01-01	2023-12-31	secondary	Portugal
3	ULSGE	Unidade Local de Saúde de Gaia/Espinho	728,107	2010-01-01	2023-12-27	secondary	Portugal
4	AP-HM	L'Assistance Publique - Hôpitaux de Marseille	2,806,891	2014-01-01	2024-02-24	secondary	France
5	COMNET MODENA	Modena Cancer Center of the AOU Polidinico	89,211	2011-01-01	2023-11-22	secondary	Italy
6	IMASIS	Hospital del Mar Electronic Health Record Information System	1,084,151	2010-01-01	2024-02-10	secondary	Spain
7	POLIMI	Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico	1,447,865	2016-01-01	2024-02-24	secondary	Italy
8	AOUPR	University Hospital of Parma	573,205	2021-01-01	2022-12-31	secondary	Italy
9	ATENEA	Marina Salud S.A. (Hospital de Denia)	356,723	2014-01-01	2024-03-26	secondary	Spain
10	AZGR	AZ Groeninge	68,918	2018-01-01	2022-12-31	secondary	Belgium
11	BARDENA	BARDENA	1,972,272	2012-01-01	2023-12-31	EHR P+S	Spain
12	BDR	Bulgarian Diabetes Register	501,065	2018-01-01	2018-12-31	registry	Bulgaria
13	BZMC	Bnai Zion Medical Center	1,075,585	2020-01-01	2024-05-05	secondary	Israel
14	CHA CAN	Charité Cancer	214,443	2010-01-01	2023-12-31	secondary	Germany
15	CHCZ	Clinical Hospital Center Zvezdara	618,992	2014-01-01	2024-07-08	secondary	Serbia
16	CPRD GOLD	Clinical Practice Research Datalink (CPRD) GOLD	17,267,137	2010-01-01	2023-06-23	primary	UK
17	CPRD Aurum	Clinical Practice Research Datalink (CPRD) Aurum	44,851,398	2010-01-01	2023-06-07	primary	UK
18	GMC	Galilee Medical Center	947,455	2013-01-01	2024-04-30	secondary	Israel
19	HULAFE	Health Department Valencia-La Fe	2,371,896	2016-01-01	2023-12-31	EHR P+S	Spain
20	HUS	Helsinki University Hospital	480,286	2010-01-01	2024-06-11	secondary	Finland
21	InGef RDB	InGef Research Database	9,111,064	2013-01-01	2023-03-31	claims P+S	Germany
22	INT	DataWareHouse of the INT – National Cancer Institute Milano	1,296,676	2010-01-01	2024-08-19	secondary	Italy
23	IPCI	The Integrated Primary Care Information	2,817,331	2010-01-01	2023-06-30	primary	Netherlands
24	ITF CDM	Istanbul University (IU) Istanbul Faculty of Medicine	899,515	2018-01-01	2021-12-07	secondary	Turkey
25	MAITT	10% random sample of complete EHR prescriptions and claims of Estonia 2012-2019	149,364	2012-01-01	2019-12-31	claims P+S	Estonia
26	UZA	University Hospital Antwerp	49,011	2018-01-01	2023-12-31	secondary	Belgium
27	MarketScan	Merative MarketScan®	176,890,290	2016-01-01	2022-09-30	claims P+S	USA
28	NCR	Netherlands Cancer Registry	2,514,888	2010-01-01	2023-01-31	registry	Netherlands
29	OLVA MS	Onze-Lieve-Vrouwziekenhuis Aalst-Asse-Ninove	51,278	2015-07-01	2024-09-10	secondary	Belgium
30	H12O	Hospital 12 Octubre	2,891,589	2011-01-01	2021-12-31	secondary	Spain
31	OPCRD	Optimum Patient Care Research Database	25,953,068	2010-01-01	2024-03-22	primary	UK
32	Clinformatics	Optum Clinformatics®	77,234,542	2016-01-01	2022-12-31	claims P+S	USA
33	PGH	Papageorgiou General Hospital	1,410,224	2010-01-01	2023-10-09	secondary	Greece
34	P+	IQVIA Pharmetrics+	159,649,500	2015-01-01	2023-07-31	claims P+S	USA
35	PRISIB	PRISIB	2,498,289	2010-01-01	2023-12-31	EHR P+S	Spain
36	ReumaPT	Rheumatic Diseases Portuguese Registry	28,325	2010-01-01	2022-05-27	registry	Portugal
37	SCIFI-PEARL	Swedish Covid-19 Investigation for Future Insights – a Population Epidemiology Approach using Register Linkage	11,686,191	2018-01-01	2023-11-29	EHR P+S	Sweden
38	SIDIAP	The Information System for Research in Primary Care	8,553,325	2010-01-01	2023-06-30	primary	Spain
39	PSSJD	Parc Sanitari Sant Joan de Déu	659,817	2017-01-01	2023-12-31	secondary	Spain
40	SUCD	Semmelweis University (SU) Clinical Database	2,075,672	2011-01-01	2022-10-10	secondary	Hungary
41	MEB KI	MEB KI	3,403,513	2010-01-01	2023-10-31	EHR P+S	Sweden
42	TAUH	Tampere University Hospital	2,878,001	2010-01-01	2023-12-22	secondary	Finland
43	THIN Belgium	THIN Belgium	2,023,580	2010-01-01	2023-12-31	primary	Belgium
44	THIN Spain	THIN Spain	1,896,031	2013-01-01	2023-12-25	primary	Spain
45	THIN France	THIN France	25,949,765	2010-01-01	2023-12-31	primary	France
46	THIN Italy	THIN Italy	1,225,836	2010-01-01	2023-12-31	primary	Italy
47	THIN Romania	THIN Romania	1,135,795	2010-01-01	2023-12-01	primary	Romania
48	THIN UK	THIN UK	10,977,326	2010-01-01	2023-12-31	primary	UK
49	UM DRESDEN	UM DRESDEN	624,697	2018-01-01	2023-12-31	secondary	Germany
50	PCASF	University of Turku	22,232	2010-01-01	2022-11-07	secondary	Finland
51	VID CONSIGN	Valencia Health System Integrated Database (VID)	1,964,588	2018-01-01	2021-12-31	EHR P+S	Spain
52	Viecuri	VieCuri Medical Center Rheumatology Database	4,918	2018-01-01	2023-07-31	secondary	Netherlands

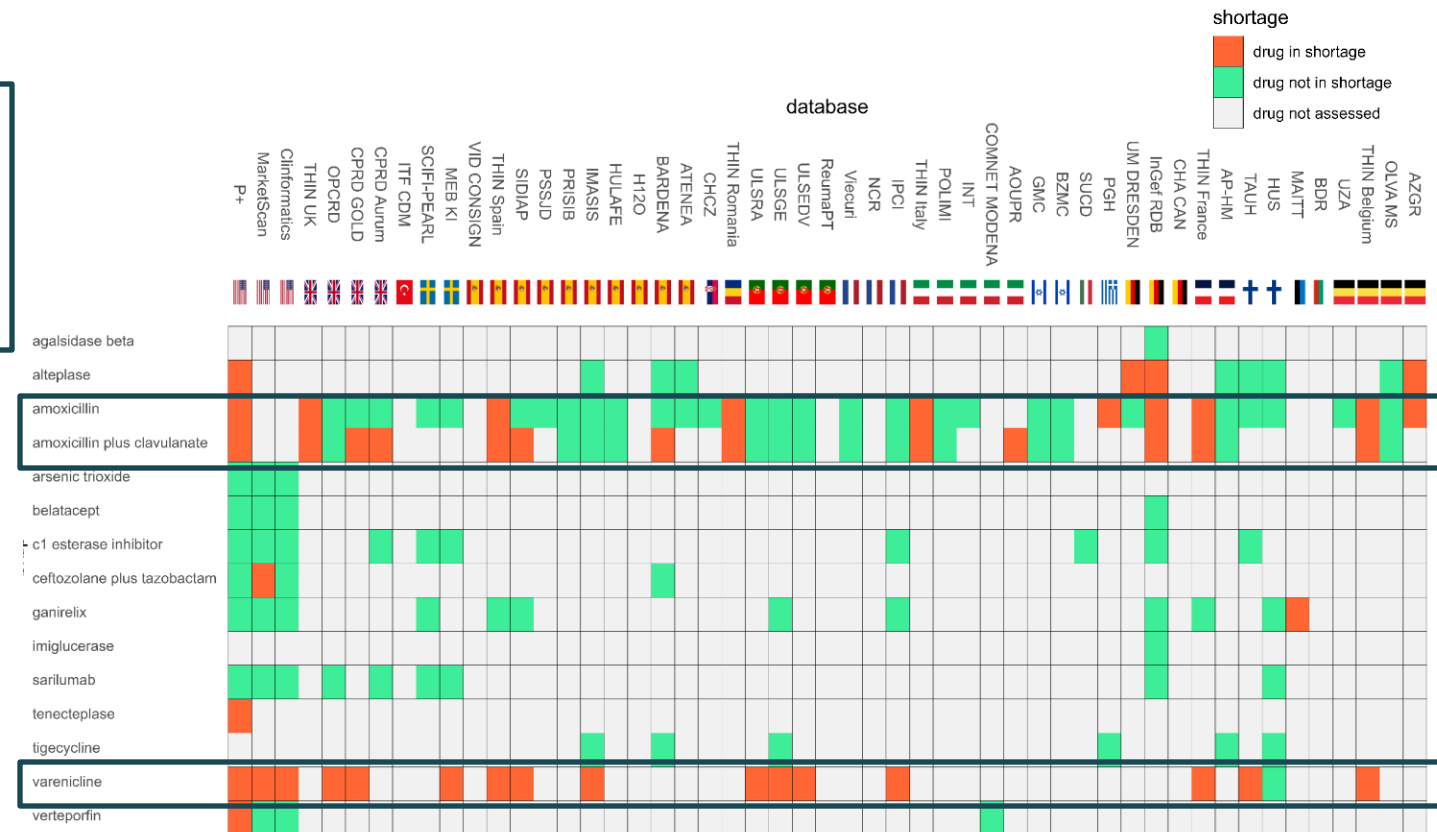
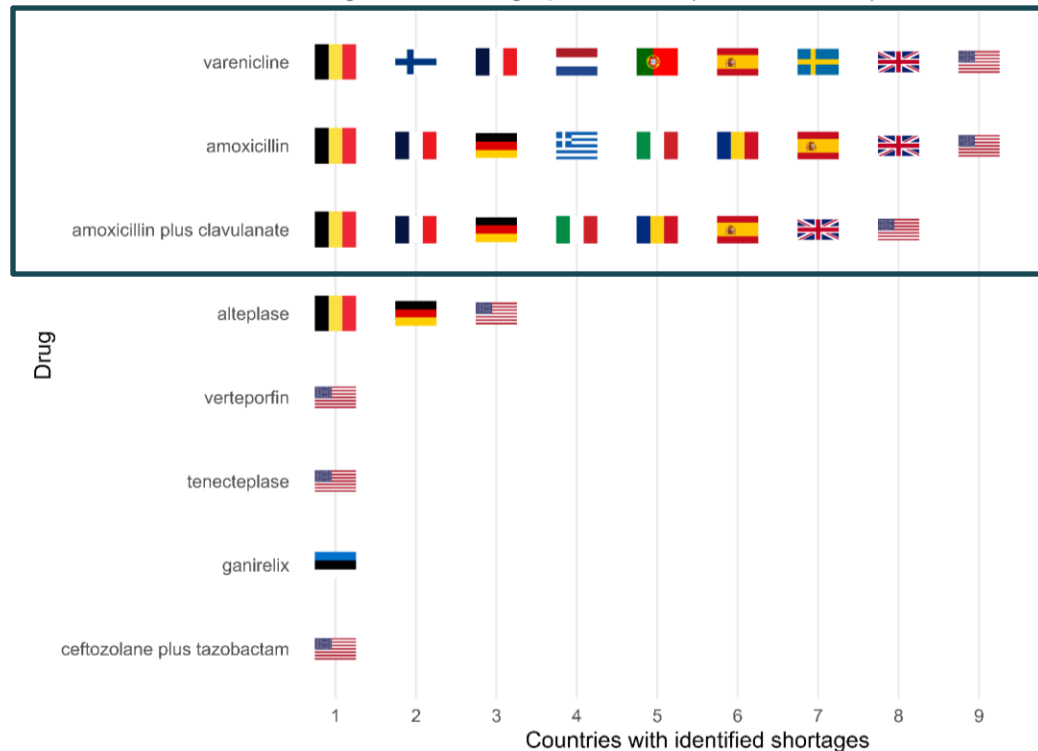


RESULTS HIGHLIGHTS

Incidence and prevalence analysis show **varenicline** and **amoxicillin (alone or with clavulanate)** were **in shortage** [drop in use of $\geq 33\%$] in the larger number of countries and databases.

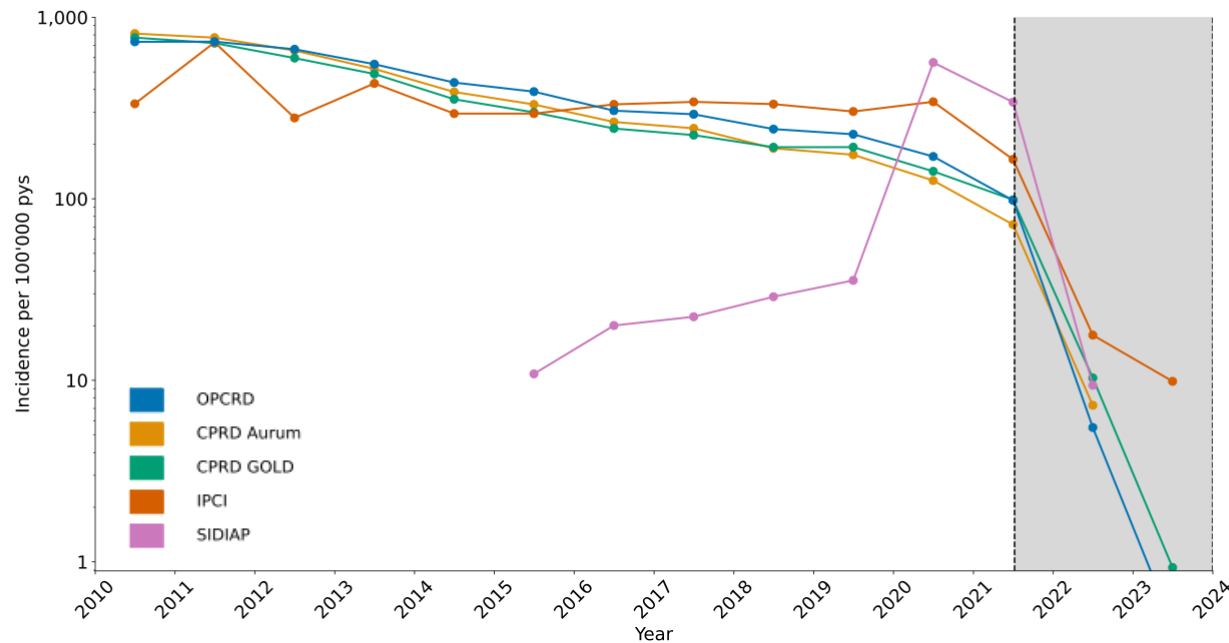
Prevalence results:

Drugs with shortage prevalence (33% threshold)





A) Primary care databases



B) Secondary care databases (hospital data)

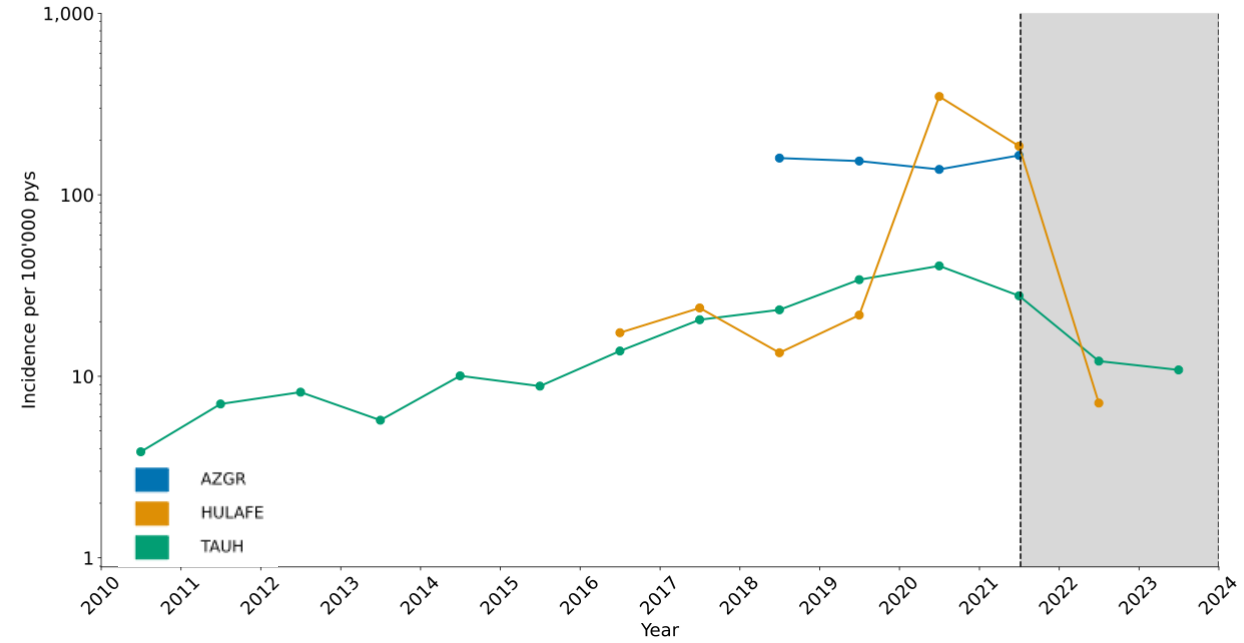


Figure 3: Incident use of varenicline in the databases showing a $\geq 30\%$ decrease after the drug shortage was announced in A) primary care databases and B) secondary care databases.

Other types of databases are shown in Figure 3C (publication), where 4 databases had $\geq 30\%$ drop in incident use of varenicline. The grey shaded area represents the period after the drug shortage was announced.



RESULTS HIGHLIGHTS

Amoxicillin (alone or with clavulanate): broad-spectrum antibiotic Shortage announced on 27th Jan 2023

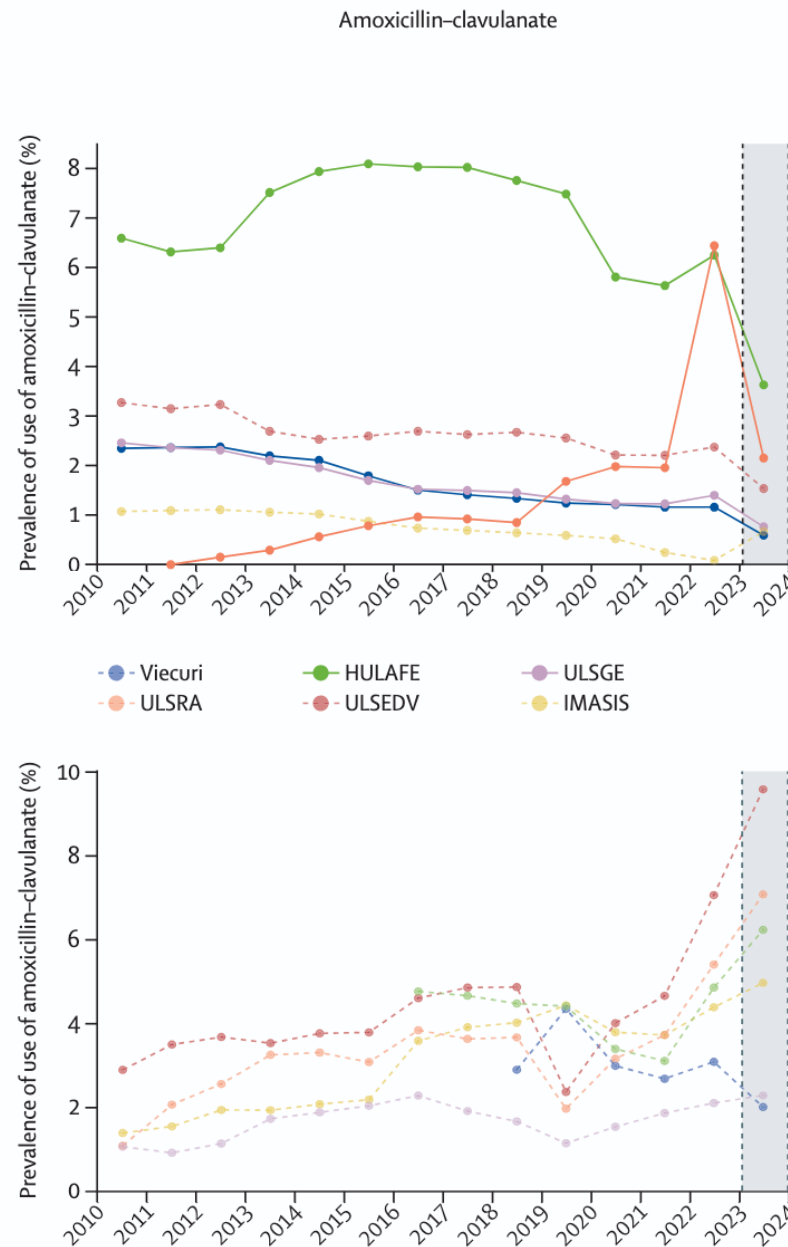
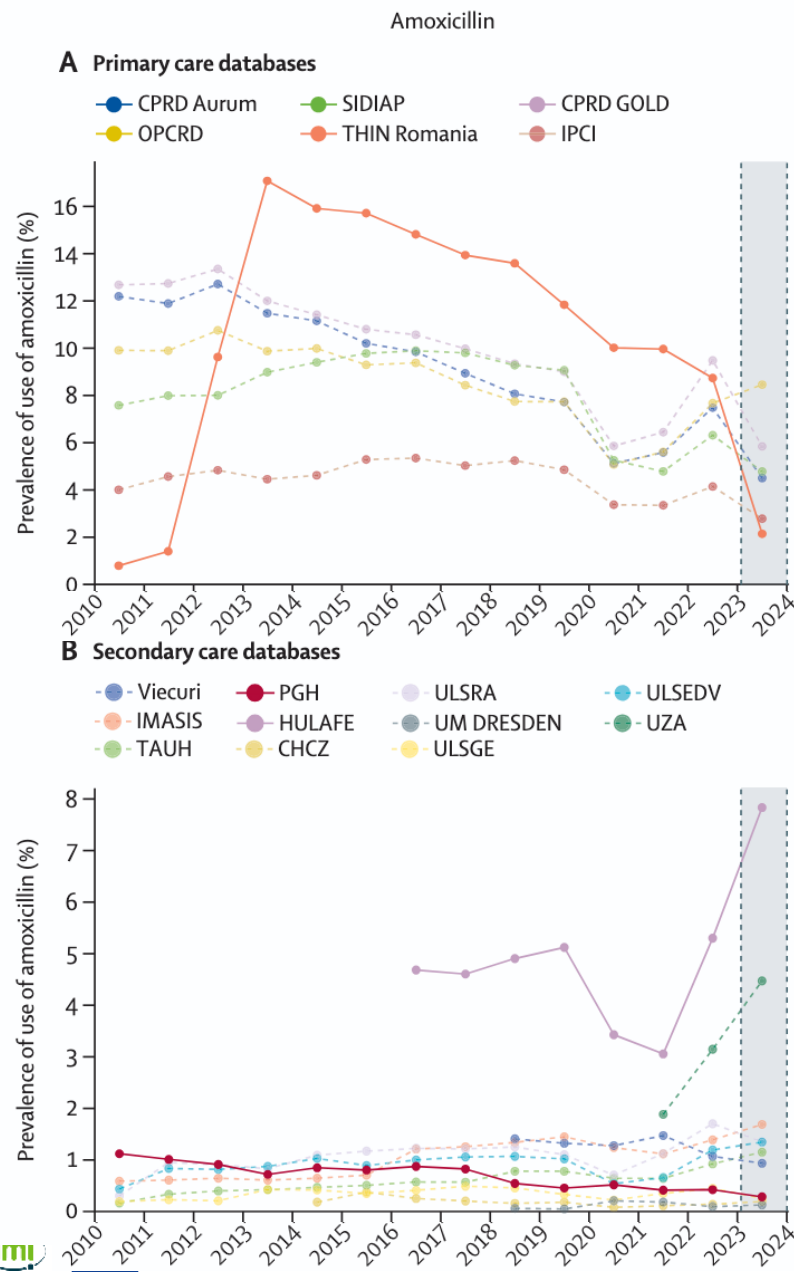


Figure 5: Prevalence of amoxicillin alone or with clavulanate in the databases showing a $\geq 30\%$ decrease after the drug shortage was announced in A) primary care databases and B) secondary care databases.

Other types of databases are shown in Figure 5C (publication), where 5 and 4 databases had $\geq 30\%$ drop in incident use of amoxicillin alone and combined, respectively. The grey shaded area represents the period after the drug shortage was announced.

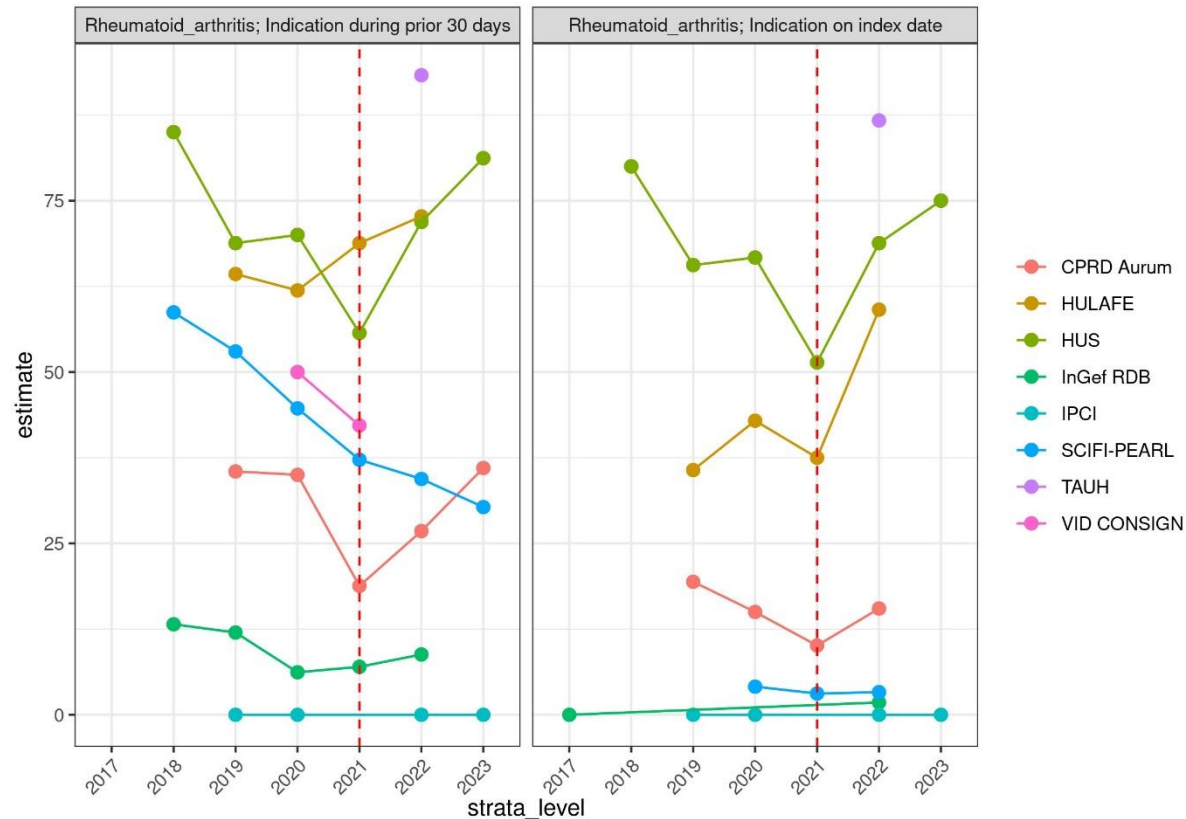


RESULTS HIGHLIGHTS

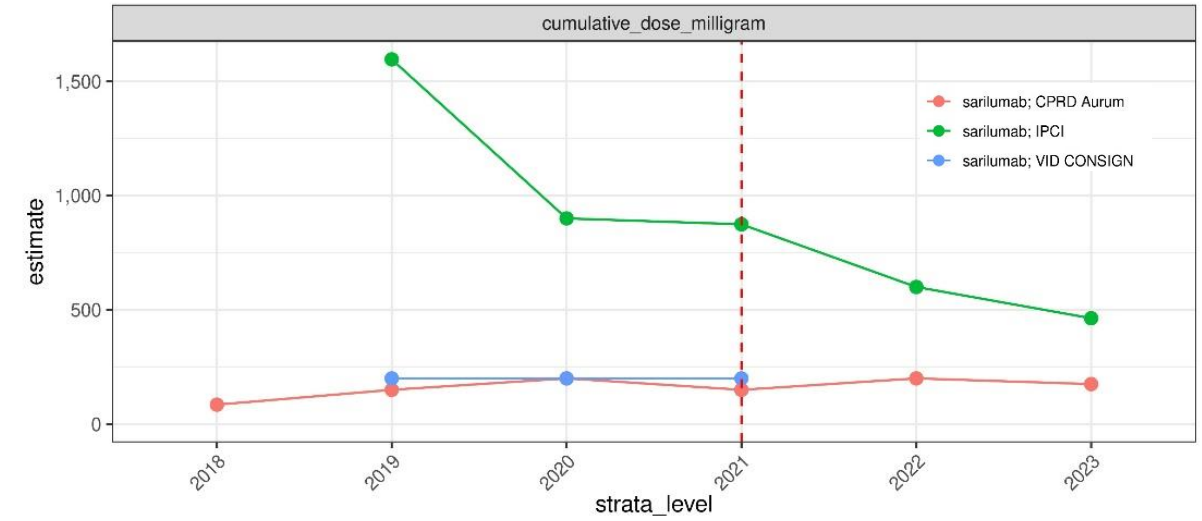
Sarilumab: IL-6 antibody to treat rheumatoid arthritis Shortage announced on 9th Nov 2021

Supplementary Figure 8) Observed changes in large-scale patient-level drug utilisation study of incident users of Sarilumab after shortage date (vertical red line):

D) Indication for Rheumatoid arthritis before prescription



G) Cumulative dose



Cumulative dose decreased in IPCI (primary care database in the Netherlands)

We observed a decrease of RA indication before shortage announcement that could be related to re-purpose for COVID-19.



- Drug shortages lead to observable changes in drug use internationally:
 - Declines in the incidence and prevalence of use
 - Modifications in drug utilisation and indication for some medicines
- Federated network analyses + OMOP-CDM enable the execution of this study in 52 databases from Europe and North America



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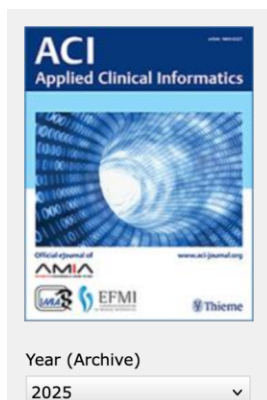
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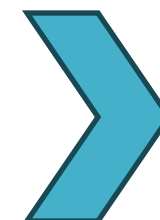
Best practices to design, plan, and execute large-scale federated analyses – key learnings and suggestions from a study comprising 52 databases

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2nd article: Learnings on
Best practice for Mega
federated analyses studies

SCAN ME





Incidence and Prevalence results:

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https://data.ehden.eu/MegaStudy_IncidencePrevalence/

Drug Utilisation results:

SCAN ME



https://data.ehden.eu/MegaStudy_Dus/



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