# SAFETY-VAC study

## Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources

Specific Contract No 02 implementing framework contract No EMA/2020/46/TDA/18

Study Report for Objective 2:
Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources
Deliverable 5 – October 2024

**Main Authors:** Carlos E. Durán, Rosa Gini, Davide Messina, Belén Castillo-Cano, Giuseppe Roberto, Fabio Riefolo, Judit Riera, Sima Mohammadi, Irene Pazos, Miriam Sturkenboom.

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|---|---|
| Document version: | 2.0 |
| First Release date: | 15 October 2024 |
| Second Release date: | 14 March 2025 |
| Final version: | 21 April 2025 |

**Disclaimer & acknowledgement**
The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network (led by Utrecht University) in collaboration with the Vaccine Monitoring Collaboration for Europe network (VAC4EU).
The scientific work for this project was coordinated by the University Medical Center Utrecht. The project has received support from the European Medicines Agency under the Framework service contract nr EMA/2020/46/TDA/L5.06.
This report expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
This study has been registered in the HMA-EMA Catalogue of Real-World Data under the EU PAS number: EUPAS1000000233.

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# 1 TITLE

SAFETY-VAC: Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources.

# 2 ABSTRACT

## 2.1 TITLE

SAFETY-VAC: Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources.

## 2.2 KEYWORDS

Chronic diseases, Symptom flare-up, Real-world evidence, Post-Authorisation, Background incidence rates.

## 2.3 RATIONALE AND BACKGROUND

The European Medicines Agency (EMA) together with the European Centre for Disease Prevention and Control (ECDC) established the Vaccine Monitoring Platform (VMP), of which one of the objectives is to generate a real-world evidence (RWE) framework for post-authorisation safety evaluation that can be leveraged in case of a new public health emergency or a safety concern occurring with a novel, or a more characterised, vaccine authorized in the European Union (EU) and the European Economic Area (EEA).
This study is part of this feasibility assessment to develop and operationalise definitions of flares of auto-immune chronic diseases and generate background incidence rates using European electronic healthcare record databases. Ten chronic inflammatory-related diseases were selected: autoimmune hepatitis (AIH), erythema nodosum (EN), Graves' disease (GD), Hashimoto´s thyroiditis (HT), multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic arthritis (PSA), polyarteritis nodose (PAN), and ulcerative colitis (UC) using 7 large European EHR data sources. The selection of these chronic conditions was made in agreement with representatives from the EMA. It was based on the limited epidemiological public evidence on the flares for the selected underlying diseases, thus the need to start building RWD epidemiological benchmarks for future association studies, and the potential impact that vaccination may have on these pre-existing conditions

## 2.4 RESEARCH QUESTIONS AND OBJECTIVES

The research question is how to estimate the background incidence of flares of selected auto-immune diseases in electronic health record data.

**Primary objective:**
To estimate the background (independent of vaccination) incidence rates of flares and the 6- and 12-month cumulative incidence of flares in patients with GD,, HT, PAN, AIH, RA, PsA, MS, EN, SLE, and UC using European electronic healthcare data sources.

**Secondary objectives:**

1. To assess the contribution of different provenances of data and the contribution of the different components of the flare definition to the incidence rates of flares.
2. To estimate the background incidence rates of flares of the selected auto-immune diseases in pregnant population.

## 2.5 STUDY DESIGN

A multi-database cohort study was conducted during the study period from January 1st, 2017, till the last data availability in each data source. We accessed data from 7 different electronic health record data sources from the EU PE&PV and VAC4EU networks of 5 European countries: BIFAP, VID, and SIDIAP from Spain, PEDIANET from Italy, SNDS from France, NHR from Norway, and CPRD from the United Kingdom.
This study estimates IRs of flares of 10 selected pre-existing chronic diseases (GD, HT, PAN, AIH, RA, PsA, MS, EN, SLE, and UC) using electronic healthcare record data sources. A clinical definition was developed for each flare event (Annex 1), and a summary of the definitions and the algorithms to identify the events is presented in Table 2.
For each disease, a study cohort of the incident diagnoses was created. Incidence rates of flares per 1,000 PY were calculated using the number of flares in the numerator applying a lag time between repeated events of at least 90 days for each cohort, except 30 days for AIH and 60 days for EN, to avoid misclassification. Kaplan-Meier analyses were conducted to calculate the cumulative incidence (incidence proportion) of a first flare at 6- and 12-months after the start of follow-up, which was censored upon the earliest of a vaccination, a flare, or the end of follow-up.
For each auto-immune condition of interest, the component strategy was applied to describe the contribution and data diversity of each component of the flare identification algorithm in a data source-specific manner.

## 2.6 RESULTS

As requested per the technical specification of the tender, for the 10 selected auto-immune diseases, the background incidence, the 6- and 12-month risk of at least one flare episode were estimated. Moreover, the risk of subsequent episodes and the flares' incidence in pregnant persons were also generated as an exploratory work. Table 1 summarizes the total number of people in the disease cohort, number of people entering the follow-up period, number and incidence rates (IRs, 1,000 PY, CI 95%) of first, second, and third flare episodes for each disease cohort.
Each of the auto-immune conditions was identified by diagnostic codes only, as per available information from the participating data sources. Demographic (age/sex) distribution of the cohorts was aligned with prior knowledge about the diseases, supporting external validity of the data.
Most of the flares were identified through medicines use. Flare rates and risks were relatively high for all diseases and varied across data sources. Rates of second and third flares in those with a prior episode decreased in general. Since the medications may also have been prescribed for other conditions, this may lead to some overestimation in flares rates.
In order to add specificity to the identification of some conditions, additional exclusion criteria to identify flares for HT, EN and MS have been applied. This decision had an

important impact on the number of individuals who participated in the cohorts for the identification of flares and the corresponding incidence calculation.
In some data sources, the specific disease could not be identified due to lack of specific codes or because the population does not have the disease (e.g., PEDIANET, which comprises only children).

*Table 1: Total number of people in the disease cohort, number of people entering the follow-up period, numbers and incidence rates (IRs, 1,000 PY, CI 95%) of first flares episodes and the 1-year flares' cumulative incidence for each disease cohort.*

| | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Record linkage requirement | 11,638,471 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sex or birth year missing or absurd or no dates of entry or exit, or incomplete date of death or birth, or less than 365 days of follow-up. | 10,941,565 | 2,975,138 | 255,180 | 1,470 | 230,032 | 3,727 | 107,103 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| ***Autoimmune Hepatitis (AIH)*** | | | | | | | |
| Total cohort, n | 2,954 | 3,276 | 1,205 | 0 | 1,935 | 640 | 1,520 |
| Persons entering follow-up, n | 2,809 | 3,214 | 1,140 | - | 1,870 | 584 | 1,472 |
| First flare-up episode, IR (CI 95%) | 401.5 (380.4-423.5) | 179.5 (169.5-190) | 459.4 (419.3-502.3) | - | 412.6 (386.9-439.7) | 307.3 (266.3-352.8) | 384.6 (355.8-415.2) |
| Second flare-up episode, IR (CI 95%) | 165.2 (148.1-183.7) | 55.8 (47.4-65.1) | 225.2 (182.4-275) | - | 184.8 (163-208.7) | 141.1 (98.3-196.3) | 168.8 (143.5-197.2) |
| Third flare-up episode, IR (CI 95%) | 80.9 (58.3-109.4) | 41.9 (22.3-71.7) | 321.9 (184-522.8) | - | 124.1 (91.8-164) | 446.4 (230.7-779.7) | 157 (108.1-220.5) |
| ***Erythema Nodosum (EN)*** | | | | | | | |
| Total cohort, n | 4,204 | NA | 25 | 5 | 120 | 420 | 7 |
| Persons entering follow-up, n | 4,100 | NA | 24 | 5 | 115 | 408 | 17 |
| First flare-up episode, IR (CI 95%) | 242.3 (231.5-253.5) | NA | 492.5 (262.2-842.2) | 0 (0-276.1) | 538.8 (422.4-677.5) | 412.3 (355.2-476) | 528.4 (171.6-1232.2) |
| Second flare-up episode, IR (CI 95%) | 89.3 (79.2-100.3) | NA | 59 (1.5-328.5) | NA | 300.9 (204.4-427.1) | 258.7 (192-341.1) | 157.6 (4-878.3) |
| Third flare-up episode, IR (CI 95%) | 47.9 (28.4-75.7) | NA | NA | NA | 145.9 (58.7-300.7) | 136.8 (59.1-269.5) | 4,198.3 (106.3-23,391.3) |
| ***Graves disease (GD)*** | | | | | | | |
| Total cohort, n | 48,857 | 48,315 | 30,168 | 5 | 40,384 | 11,334 | 16,793 |
| Persons entering follow-up, n | 45,476 | 45,943 | 27,642 | 5 | 37,876 | 9,807 | 15,908 |
| First flare-up episode, IR (CI 95%) | 118.5 (116.2-120.7) | 0.1 (0-0.2) | 11.8 (10.7-13.1) | 227.4 (5.8-1267.1) | 101.2 (98.9-103.4) | 104.9 (99.5-110.4) | 25.1 (23.4-26.9) |
| Second flare-up episode, IR (CI 95%) | 355.6 (345.2-366.2) | 102.3 (12.4-369.4) | 71 (39.7-117.1) | 3069.3 (77.7-17101.2) | 438 (423.9-452.5) | 392.1 (355.8-431.2) | 105.9 (87.5-127.1) |
| Third flare-up episode, IR (CI 95%) | 472.4 (451.6-494) | 0 (0-1570.4) | 0 (0-854.4) | 8494.2 (215.1-47326.6) | 567.4 (541.2-594.5) | 713.4 (602-839.5) | 157.5 (96.2-243.2) |
| ***Hashimoto thyroiditis (HT)*** | | | | | | | |
| Total cohort, n | 9,119 | NA | NA | 15 | 2,549 | 958 | NA |
| Persons entering follow-up, n | 8,585 | - | - | 11 | 2,517 | 890 | - |
| First flare-up episode, IR (CI 95%) | 107.5 (102.7-112.4) | - | - | 110.6 (13.4-399.6) | 186.7 (174.8-196.6) | 67.8 (54.8-82.9) | - |
| Second flare-up episode, IR (CI 95%) | 1.8 (0.8-3.5) | - | - | 0 (0-1,096.3) | 0 (0-1.8) | 0 (0-35.7) | - |
| Third flare-up episode, IR (CI 95%) | 151.9 (3.8-846.2) | - | - | - | - | - | - |
| ***Multiple sclerosis (MS)*** | | | | | | | |
| Total cohort, n | 6,555 | 720 | 186 | - | - | 2,860 | - |
| Persons entering follow-up, n | 6,207 | 713 | 174 | - | - | 2,622 | - |
| First flare-up episode, IR (CI 95%) | 25 (22.6-27.6) | 400.4 (367-436.1) | 396.5 (307.3-503.5) | - | - | 256.5 (239.4-274.5) | - |
| Second flare-up episode, IR (CI 95%) | 169.2 (136.7-207.1) | 81.3 (65.5-99.7) | 91.9 (33.7-200.1) | - | - | 524.3 (468.8-584.5) | - |
| Third flare-up episode, IR (CI 95%) | 418 (295.8-573.7) | 64.2 (29.4-121.9) | 0 (0-859.3) | - | - | 1115.9 (943.4-1310.9) | - |
| ***Systemic Lupus Erythematosus (SLE)*** | | | | | | | |
| Total cohort, n | 6,261 | 5,949 | 3,899 | 0 | 6,213 | 1,901 | 2,169 |

| | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Persons entering follow-up, n | 5,833 | 5,659 | 3,611 | - | 5,831 | 1,710 | 2,048 |
| First flare-up episode, IR (CI 95%) | 319.3 (307.5-331.5) | 175.8 (168.6-183.2) | 354.6 (335.9-374) | - | 343.4 (331-356.1) | 518.8 (484.8-554.5) | 257.4 (239.7-276) |
| Second flare-up episode, IR (CI 95%) | 182.3 (169.1-196.2) | 118.5 (108.5-129.2) | 172.9 (148.4-200.3) | - | 171.1 (159-183.9) | 292.9 (257-332.5) | 167.4 (143-194.7) |
| Third flare-up episode, IR (CI 95%) | 128.2 (106.1-153.5) | 104.8 (84.3-128.6) | 141.1 (75.1-241.3) | - | 128.3 (107.1-152.4) | 272.3 (198.6-364.4) | 222.9 (156.9-307.2) |
| ***Rhematoid Arthritis (RA)*** | | | | | | | |
| Total cohort, n | 22,039 | 55,568 | 15,992 | 6 | 17,444 | 11,884 | 40,406 |
| Persons entering follow-up, n | 20,349 | 53,263 | 14,674 | 6 | 16,033 | 10,427 | 38,231 |
| First flare-up episode, IR (CI 95%) | 315.4 (308.9-321.9) | 225.9 (223-228.7) | 359.6 (350-369.5) | 313.7 (38-1133) | 312.7 (305.5-320) | 425.7 (413.3-438.5) | 259.8 (255.6-264.1) |
| Second flare-up episode, IR (CI 95%) | 170.3 (163.3-177.6) | 148.7 (145.1-152.3) | 183.4 (170.2-197.4) | 0 (0-481.7) | 165 (157.3-173) | 261.3 (245.5-277.9) | 148.2 (142.9-153.7) |
| Third flare-up episode, IR (CI 95%) | 120.9 (108.4-134.5) | 139 (131.9-146.4) | 175.2 (134.3-224.6) | - | 111.6 (98.3-126.1) | 242.5 (208.2-280.9) | 175.6 (161.2-191) |
| ***Psoriatic arthritis (PSA)*** | | | | | | | |
| Total cohort, n | 3,348 | 21,070 | 4,292 | 0 | 6,380 | 1,413 | 10,338 |
| Persons entering follow-up, n | 3,050 | 20,164 | 3,868 | - | 5,962 | 1,243 | 9,768 |
| First flare-up episode, IR (CI 95%) | 269 (254.3-284.3) | 232.4 (227.7-237.1) | 380.2 (360.8-400.4) | - | 281.8 (271-292.9) | 541.1 (499.5-585.3) | 320.9 (311.2-330.7) |
| Second flare-up episode, IR (CI 95%) | 146.6 (129.4-165.5) | 147 (141.4-152.7) | 206.1 (178.9-236.3) | - | 136.8 (125.6-148.9) | 335.2 (287.6-388.4) | 161.8 (151.5-172.6) |
| Third flare-up episode, IR (CI 95%) | 84.6 (55.2-123.9) | 117.4 (107.2-128.3) | 156.2 (91-250) | - | 55.2 (40.3-73.9) | 274.9 (191.5-382.3) | 124.4 (104.2-147.3) |
| ***Polyarteritis Nodose (PAN)*** | | | | | | | |
| Total cohort, n | 450 | 199 | 439 | 0 | 331 | 141 | 201 |
| Persons entering follow-up, n | 407 | 188 | 423 | - | 296 | 127 | 176 |
| First flare-up episode, IR (CI 95%) | 80.9 (62.1-103.5) | 0 (0-5.7) | 38.4 (25.3-55.8) | - | 88.8 (66.3-116.4) | 142.9 (90.6-214.4) | 131.7 (92.3-182.4) |
| Second flare-up episode, IR (CI 95%) | 88.8 (38.3-174.9) | - | 75.5 (9.1-272.6) | - | 61 (19.8-142.3) | 625.1 (285.8-1186.6) | 172.2 (78.7-326.9) |
| Third flare-up episode, IR (CI 95%) | 227.6 (27.6-822.1) | - | 0 (0-12030) | - | 659 (179.6-1687.3) | 1808.2 (372.9-5284.2) | 284.3 (58.6-830.9) |
| ***Ulcerative Colitis (UC)*** | | | | | | | |
| Total cohort, n | 9,491 | 32,292 | 7,196 | < 5 | 10,603 | 6,535 | 15,299 |
| Persons entering follow-up, n | 4,887 | 6,134 | 1,679 | < 5 | 5,673 | 3,918 | 3,368 |
| First flare-up episode, IR (CI 95%) | 222.7 (215.3-230.2) | 129.3 (126.7-131.8) | 202.7 (193.5-212.3) | 9131.2 (1105.8-32985.2) | 212.2 (205.5-219) | 384.9 (370.9-399.4) | 162.2 (157.4-167.2) |
| Second flare-up episode, IR (CI 95%) | 176.3 (164.8-188.4) | 128.1 (123-133.4) | 363.9 (329.4-401) | 0 (0-654.4) | 158.5 (148-169.5) | 271.6 (251.7-292.7) | 153.9 (143.7-164.6) |
| Third flare-up episode, IR (CI 95%) | 187.9 (162-216.9) | 183.7 (169-199.4) | 687.9 (557.2-840.1) | - | 209.7 (181-241.7) | 378.8 (321.3-443.6) | 194.1 (165.6-226.1) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

## 2.7 CONCLUSION

This study aimed to generate background incidence rates and 6- and 12-month risk of flares of 10 selected auto-immune diseases. Flare rates were relatively high in all conditions, although they varied across data sources. Rates of second and third flares in those with a prior episode decreased in general. Flare events were mostly identified throughout medication use (start of a new drug), which may introduce some overestimation due to the use of the drugs in other indications. While limited information on the incidence or risk of flares for the selected diseases is available in the literature for comparison or validation, this study creates a benchmark for future research in this area.

# 3 MARKETING AUTHORISATION HOLDER

Not applicable (NA)

# 4 INVESTIGATORS

| | |
|---|---|
| University Medical Center Utrecht (UMCU), Utrecht, The Netherlands | Dr. Carlos E. Durán,<br>Prof. Dr. Miriam Sturkenboom,<br>Drs. Judit Riera<br>Drs. N Luxi |
| Universiteit Utrecht (UU), Utrecht, The Netherlands<br>CPRD data | Prof. Dr. Olaf Klungel,<br>Dr. Patrick Souverein,<br>Dr. Helga Gardarsdottir |
| VAC4EU | Drs. Sima Mohammadi<br>Dr. Daniel Weibel |
| Teamit Institute | Dr. Fabio Riefolo,<br>Dr. Irene Pazos |
| Agenzia Regionale di Sanitá Toscana (ARS)<br>Data Tuscany region | Dr. Rosa Gini,<br>Davide Messina,<br>Dr. Giuseppe Roberto<br>Anna Girardi<br>Giulia Hyeraci |
| Società Servizi Telematici -Pedianet | Prof. Dr. Carlo Giaquinto,<br>Dr. Elisa Barbieri,<br>Luca Stona |
| Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAP JGol) | Dr. Felipe Villalobos,<br>Dr. Martín Solórzano<br>Carlo Alberto Bissacco |
| Instituto Aragonés de Ciencias de la Salud (IACS) | Dr. Antonio Gimeno,<br>Dr. Beatriz Poblador,<br>Dr. Mercedes Aza,<br>Dr. Aida Moreno,<br>Alejandro Santos |
| Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital | Prof. Vera Ehrenstein,<br>Lise Skovgaard Svingel,<br>Benjamin Randeris Johannesen |
| Bordeaux PharmacoEpi platform (BPE) & ADERA | Dr. Cécile Droz-Perroteau,<br>Laure Carcaillon-Bentata,<br>Jeremy Jove |
| University of Eastern Finland | Prof. Anna-Maija Tolppanen,<br>Prof. Sirpa Hartikainen,<br>Dr. Thuan Vo,<br>Dr. Anne Paakinaho,<br>Blair Rajamaki |
| University of Oslo (UiO), Norway<br>Norwegian linked registry data | Prof Dr. Hedvig ME.Nordeng,<br>Dr. Mahmoud Zidan |
| Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) – Valencia health system Integrated Database (VID) | Dr. Juan José Carreras Martínez,<br>Dr. Arantxa Urchueguía Fornes,<br>Elisa Correcher Martínez,<br>Dr. Javier Díez-Domingo |
| Spanish Agency on Medicines and Medical Devices (AEMPS) -BIFAP database | Dr. Mar Martin,<br>Dr. Patricia Garcia-Poza,<br>Dr. Airam de Burgos,<br>Belén Castillo-Cano,<br>Dr. Elisa Martín-Merino |

# 5 MILESTONES

| | |
|---|---|
| Start of project | 15 Feb 2024 |
| D1 Project planning virtual meeting | 28 Feb 2024 |
| D3 Study protocol for Objective 2 acceptance | 31 May 2024 |
| D5 Study report for Objective 2 | 15 Oct 2024 |

# 6 RATIONALE AND BACKGROUND

The COVID-19 pandemic emphasized the public health need for comprehensive and rapid post-authorisation vaccine safety surveillance. An increasing number of vaccine products are based on novel technologies, for which safety experience is limited to pre-authorisation clinical trials. While new safety concerns are expected to arise with these novel vaccines, continuous monitoring and evaluation throughout the entire lifecycle remains necessary for authorized vaccines (1,2). To this aim, networks of real-world data sources that are fit-for-purpose are essential, offering up-to-date data that can be readily accessed.

In May 2022, the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) established the Vaccine Monitoring Platform (VMP) with the aim of generating Real-World Evidence (RWE) on the safety and effectiveness of vaccines in the European Union (EU) and European Economic Area (EEA) (3). The VMP research agenda, endorsed in July 2023 by the Immunisation and Vaccine Monitoring Advisory Board (IVMAB), confirmed the need for RWE capacity, capability and readiness to allow the timely evaluation of vaccines. Therefore, the EMA required the service of a contractor to provide a framework for post-authorisation safety evaluation that can be leveraged in case of a new public health emergency or a safety concern occurring with a novel or a more characterised vaccine. This study is part of this feasibility assessment, to assess whether background incidence rates of flares of selected chronic diseases using electronic healthcare record databases can be generated.

Literature suggests that COVID-19 vaccines (4,5) and the recombinant zoster vaccine (6) may trigger flares of immune-mediated inflammatory diseases, but causality has not been proved, and study results remain contradictory (5,7–13). In general, a flare-up is a transient exacerbation of symptoms of an existing disease or condition. Traditionally, flares have been investigated through direct questionnaires to patients and/or physicians. In the context of Real-World Data (RWD) observational studies, identifying and comparing the incidence of adverse events following exposure, such as flaring up of pre-existing underlying diseases, with baseline incidence rates (IRs) in a target population is crucial to monitor the safety of medicinal products. Capturing and accessing accurate background IRs of adverse events is essential for contextualizing vaccine safety signals, such as through observed-to-expected analysis (14–17). Measuring flares of chronic immune-mediated disease in electronic health record data sources is challenging for several reasons; for instance, in electronic health records, there is, most of the time, an adequate registration of the date of diagnoses. However, there is no proper tracking of the disease evolution (ending, worsening, flares, etc), the flares may be diagnosed/treated in a different clinical setting (e.g., GP) than where it was originally diagnosed, and multiple data sources need to be consulted.

In this study, ten chronic conditions were selected to investigate the background occurrence (i.e. not associated to vaccine exposure) (16) of flares identified in European

electronic health care record databases. The selection of these conditions was made in agreement with representatives from the EMA. It was based on the limited epidemiological publicised evidence on the flares for the selected underlying diseases, thus the need to start building RWD epidemiological benchmarks for future association studies, and the potential impact that vaccination may have on these pre-existing conditions. Additionally, an analysis of the different components of the proposed algorithms to identify flare episodes was performed. This analysis allows to describe the contribution of each component of the flare identification algorithm in a data source-specific manner, assessing the impact of adding different components of information to the identification of cases in relation to the specific provenance of the data. This strategy facilitates the interpretation of study findings (18).

# 7 RESEARCH QUESTION AND OBJECTIVES

The overarching goal of the SAFETY-VAC project is to create a framework for the post-authorisation safety monitoring and evaluation of vaccines in Europe that can conduct near real-time studies on new or existing vaccines.

The research question of this report is to report how the background incidence rates (IR) of flares of 10 selected auto-immune diseases in electronic health record data can be estimated. *Background rate* is defined as the rate of an event occurring in the absence of vaccination during the study period.

**Primary objective:**
To estimate the background incidence rates of flares and 6- and 12-month cumulative incidence of flares in patients with Graves´ disease (GD), Hashimoto´s thyroiditis (HT), polyarteritis nodosa (PAN), autoimmune hepatitis (AIH), rheumatoid arthritis (RA), psoriatic arthritis (PsA), multiple sclerosis (MS), erythema nodosum (EN), systemic lupus erythematosus (SLE), and ulcerative colitis (UC) using 9 European electronic healthcare data sources

**Secondary objective(s):**
1. To assess the contribution of different provenances of data and the contribution of the different components of the flare definition to the incidence rates of flares.
2. To estimate the background incidence of flares of selected auto-immune diseases in the pregnant population.

# 8 AMENDMENTS AND UPDATES OF THE PROTOCOL

| Number Amendment | Document Amended | Reason | Approval Date |
|---|---|---|---|
| 1 | D3 Study protocol for Objective 2 | Implementation of exclusion criteria for some flares algorithms | 2024, Sep 31st |

# 9 RESEARCH METHODS

## 9.1 STUDY DESIGN

A population-based multi-database cohort study was conducted during the period from January 1st, 2017, till the last data availability, specific for each data source (see Table 5). Ten study cohorts of incident diagnoses of the selected auto-immune diseases were constructed.

## 9.2 SETTING

The study was conducted using electronic health record data from 7 data sources in 5 European countries [Spain: SIDIAP (Catalonia), VID (Valencia region) and BIFAP (several regions); Norway: Norwegian National Registers; Italy: PEDIANET; France: SNDS (10% sample of national registries), and United Kingdom: CPRD (national)], see section 9.4 for further details on data sources. These data sources proved to have data instances ready to carry out this study (19).

### 9.2.1 Subjects:

The source population comprises all persons included in the data sources. The study population was selected from the source population after the application of the inclusion and exclusion criteria. Ten incident disease-specific study cohorts were created, one for each auto-immune disease: Graves' disease, Hashimoto´s thyroiditis, polyarteritis nodosa, autoimmune hepatitis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, erythema nodosum, systemic lupus erythematosus, and ulcerative colitis.

Subjects were included in the disease-specific incident cohorts if they had, as per study protocol (20):

- At least 1 day of observation after 1 January 2017.
- A first recorded diagnosis of the disease of interest after 1 January 2017.

Subjects were excluded when:

- No birth year and sex information.
- Less than 365 days look-back at the first identification of the disease, for those not born in the study period.
- Persons with a diagnosis indicating that the disease is prevalent/chronic at first identification.

Additional exclusion criteria were implemented for the cohorts of Hashimoto thyroiditis, multiple sclerosis and erythema nodosum during any time prior:

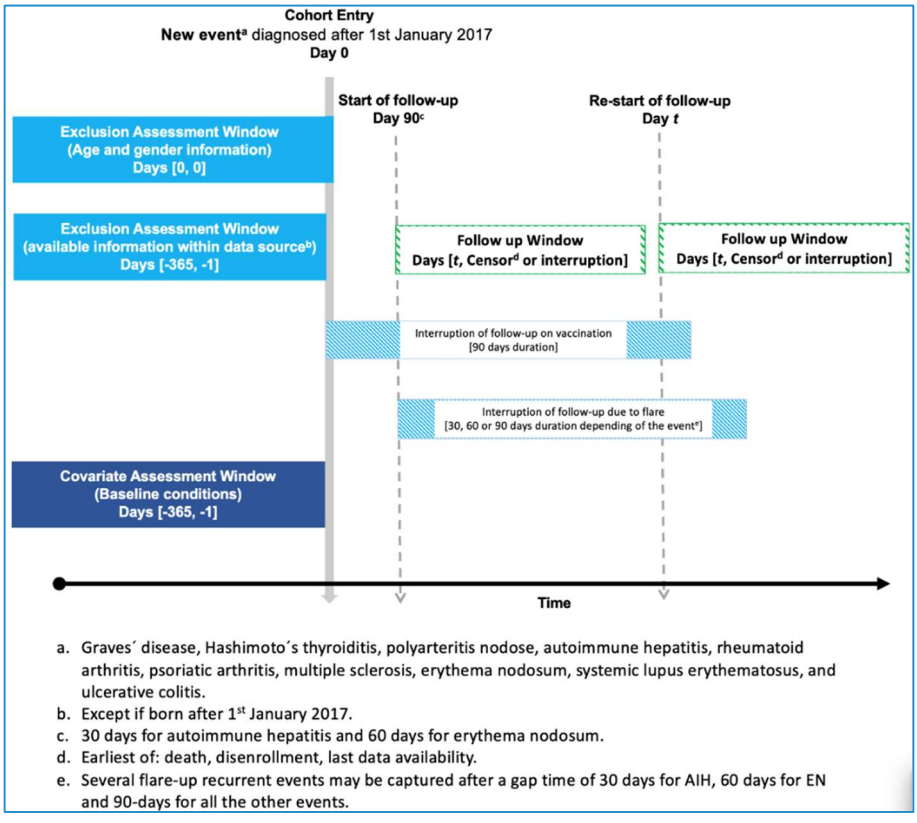
- For Hashimoto thyroiditis (HT), all persons having levothyroxine use registered within the look-back period were excluded.
- For multiple sclerosis (MS), all persons having interferon beta 1a and 1b, glatiramer and teriflunomide use registered within the look-back period were excluded.
- For erythema nodosum (EN), all persons having any panniculitis, including Löfgren syndrome diagnoses identified within the look-back period were excluded.

### 9.2.2 Follow-up

Follow-up has started when subjects had completed 90 days of follow-up after the disease diagnosis (cohort entry – day 0), except for autoimmune hepatitis and erythema nodosum where follow-up started 30, and 60 days after the diagnosis, respectively. This delay is needed for the first (diagnostic) episode to be ended and to allow the person to be at risk of a flare up. Upon each flare, the same eligibility delay for the next flare was applied.

Follow-up was interrupted when vaccination with any vaccine of interest (see subheading *vaccines* under section 9.4. Variables) occurred, from the date of vaccination to 90 days later (to ensure the flare is not recorded in the post-vaccination risk windows) (20), and finished at death, disenrollment, or last data extraction. If follow-up was interrupted because of a recorded vaccination, follow-up resumed on day 91 after vaccination until follow-up finished or was stopped again. An interruption of follow-up also happened upon a flare, with the same eligibility period as after the first diagnosis. If a vaccination was recorded during the eligibility interruption, the maximum duration of interruption (eligibility and post-vaccination) was used. The occurrence of a flare of the corresponding event was not considered a censoring criterion since a new flare can occur after a gap of 90 days (30 days for EN, and 60 for AIH). For estimation of cumulative incidence, the follow-up was censored upon the earliest of a vaccination, a flare, or the end of follow-up. See **Figure 1**.
Pregnancy population was selected through the application of the ConcePTION pregnancy algorithm (21).

*Figure 1. Representation of study participants eligibility and follow-up during the study period.*



## 9.3 VARIABLES

***Outcomes***

This study provided an estimation of IRs of flares of 10 selected pre-existing chronic diseases (GD, HT, PAN, AIH, RA, PsA, MS, EN, SLE, and UC) using electronic healthcare record data sources. A clinical event definition form was developed for each event, see **Annex 1.** Table 2 presents a summary of the event definitions, the flare definitions, and the proposed operationalization algorithms to identify the occurrence of flares in the data sources. The algorithms to identify flares presented in Table 2 are based on the current availability of the ConcePTION CDM to ETL healthcare-related information. For instance, we have used the start of a new drug treatment as a proxy of the flare, increases in doses cannot be done reliably, since many Data Experts and Access Providers (DEAPs) do not have posology data and it has not been ETL´ed.

The event definitions are presented in the protocol (20) and were further developed during the study. The event definition forms were created by the central study team, together with a representative of the VAC4EU code list task force, and University Hospitals of the University of Verona (Italy), University of Padova (Italy), Vall d'Hebron Research Institute (Barcelona, Spain), and the Drug Safety Research Unit (UK).

To create the incident disease-specific study cohorts (see section 9.2.1), code lists created and provided by VAC4EU were used. Briefly, study variables are named in a standard VAC4EU hierarchical fashion based on the body system. Each code within the code list is tagged as *narrow* or *possible* by two medical reviewers from the VAC4EU code list taskforce based on standard VAC4EU work instructions. Comments are consolidated and discussed in the VAC4EU medical code list taskforce. The code lists are subsequently compiled in a CSV file through a standard R code. This is the output included in the analysis script.

For each flare-up identification algorithm, a component strategy was applied to describe the impact of the different components of the event identification strategy on the observed rates of flares in each data source. A detailed description of the component analysis strategy is presented in section 9.8.

*Table 2. Clinical definition of the events and flare-up operationalization.*

| Event | Clinical definition | Flare-up definition | Flare-up algorithm* |
|---|---|---|---|
| Graves' disease (GD) | GD is a common form of hyperthyroidism with a diffuse hyperplastic goiter. It is an autoimmune disorder that produces thyrotropin-receptor antibodies (TRAb) against the thyroid stimulating hormone (TSH) receptor. These autoantibodies activate the TSH receptor, thereby stimulating the thyroid gland and hypersecretion of thyroid hormones. | A flare-up/relapse of GD can be defined as both, the worsening of hyperthyroidism symptoms and thyroid hormones in patients with GD who are currently undergoing medical treatment, and the re-occurrence of hyperthyroidism symptoms and thyroid hormones in patients with GD after completion of medical treatment. | Graves´ disease diagnosis (through diagnosis codes) **AND** at least 90 days after (22):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Prescription or dispensing of antithyroid drugs (ATD) after a period of 90 days of no drug exposure [MED], OR<br>• Radioactive iodine ablation after a period of >90 days after last ATDs prescription or dispensing [DIA], OR<br>• Thyroidectomy (through procedure codes) after a period of >90 days since last ATDs prescription or dispensing [PROC], OR<br>• Thyroid storm (through code list) [DIA], OR<br>• Any emergency room visit [ER], or hospitalization [H] related to Graves' disease (primary diagnosis). |
| Hashimoto's thyroiditis (HT) | HT is an autoimmune disease in which thyroid cells are destroyed via cell- and antibody-mediated immune processes. It is characterized by the presence of high serum thyroid autoantibodies, goitre and hypothyroidism. | A HT flare-up is a period of worsening and intense hypothyroidism symptoms. HT flare-up can seldomly be characterized by a hyperthyroid state. | Diagnosis of HT (through diagnosis codes) **AND** (at least 90 days after) (9):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Start of levothyroxine use (evidence of no use of levothyroxine since the disease diagnosis) [MED], OR<br>• Any emergency room visit [ER], or hospitalization [H] related to HT (primary diagnosis). |
| Polyarteritis nodosa (PAN) | PAN is a rare form of necrotizing non-granulomatous inflammation occurring primarily in medium-sized arteries, often with microaneurysms. It is characterized by muscle, joint, and abdominal pain resulting from arterial infarction and scarring in affected organs, neurological and cutaneous symptoms. | PAN relapse is defined as recurrence or new onset of disease attributable to active vasculitis. Relapse is defined as the reappearance of manifestations attributable to active vasculitis occurring after at least one-month symptom-free period. | Diagnosis of PAN (using diagnosis codes) AND (at least 90 days after (23)):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Switch from a corticosteroid to another immunosuppressant drug [MED], OR<br>• Any emergency room visit [ER], or hospitalization [H] related to PAN (primary diagnosis). |
| Autoimmune hepatitis (AIH) | AIH is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum immunoglobulin G (IgG) levels. The disease | The exacerbation of autoimmune hepatitis refers to a sudden and marked increase in inflammatory activity in the liver. This exacerbation can | Diagnosis code of AIH **AND** (at least 30 days after):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR |

| Event | Clinical definition | Flare-up definition | Flare-up algorithm* |
|---|---|---|---|
| | may start as acute hepatitis or asymptomatic increase of liver enzymes, that can lead to the development of liver cirrhosis. | manifest with an elevation of liver enzymes and IgG in blood tests with or without symptoms. | • Initiation of glucocorticoids, mycophenolate mofetil, tacrolimus, sirolimus, everolimus, antiTNF, rituximab or cyclosporin [MED], OR<br>• Any hospitalization [H], or emergency room visit [ER] related to AIH (primary diagnosis).<br><br>**NOT**<br>• Diagnosis code of hepatitis infectious in the last 30 days.<br>• Diagnosis code of alcoholic liver disease in the last 30 days.<br>• Presence of dispensing or prescription of any drug with a DILI rank as "Most-DILI concern" (24) in the last 30 days. |
| Rheumatoid arthritis (RA) | RA is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. The cause of RA is unknown. RA is considered an autoimmune disease. | RA flare-up generally refers to a worsening of symptoms/disease activity (e.g., increased joint pain, swelling, stiffness, and fatigue) following a period of partial or complete remission that would, if persistent or of sufficient duration/intensity, in most cases lead to initiation, change or increase in therapy as cannot be self-managed. | Diagnosis of RA (using diagnosis codes) **AND** (at least 90 days after diagnosis (25–27)):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Any initiation of a NSAID [MED], OR<br>• Any initiation of a corticosteroids (16,17) [MED], OR<br>• Any initiation of any Disease-modifying antirheumatic drugs (DMARDs) (conventional nonbiologic/ synthetic, targeted synthetic, or biologic) [MED], OR<br>• Identification of a code related to RA complications (scleritis, tunnel carpal syndrome, cervical myelopathy, Felty syndrome, rheumatoid vasculitis, pleuritis, pericarditis, rheumatoid nodules) if no similar code has been identified in the previous 90 days [DIA], OR<br>• Any hospitalization [H], or emergency room visit [ER] related to RA (primary diagnosis). |
| Psoriatic arthritis (PsA) | PsA is a type of inflammatory arthritis associated with psoriasis, whose main clinical manifestations are peripheral arthritis, dactylitis, enthesitis and axial involvement. It is characterized by the presence of HLA-B27-associated spondyloarthropathy, and the absence of rheumatoid factor. | PsA flare-up can be broadly considered as a period of worsening in disease activity, with significant effect on patients' quality of life. | Diagnosis of PsA (using diagnosis codes) **AND** (at least 90 days after):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Any initiation of a NSAID [MED], OR<br>• Any initiation of a corticosteroids [MED], OR<br>• Any initiation of any DMARDs (conventional nonbiologic/ synthetic, targeted synthetic, or biologic) [MED], OR<br>• Adding any DMARDs to preexisting treatment [MED], OR |

| Event | Clinical definition | Flare-up definition | Flare-up algorithm* |
|---|---|---|---|
| | | | • Any hospitalization [H] or emergency room visit [ER] related to PsA (primary diagnosis). |
| Multiple sclerosis (MS)*<br><br>*Excluding primary progressive MS (PPMS) | MS is an autoimmune disorder mainly affecting young adults and characterized by destruction of myelin in the central nervous system (CNS). Pathologic findings include multiple sharply demarcated areas of demyelination throughout the white matter of the CNS. Clinical manifestations include visual loss, extra-ocular movement disorders, paraesthesia, loss of sensation, muscle weakness, dysarthria, spasticity, ataxia, and bladder dysfunction. The usual pattern is one of recurrent attacks followed by partial recovery, but acute fulminating and chronic progressive forms also occur. | A monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection (28). | Diagnosis code of MS (using diagnosis codes) **AND** (at least 90 days after (29)):<br>• Identification of a general code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Any hospitalization [H] or emergency room visit [ER] related to MS (primary diagnosis), OR<br>• Any initiation of interferon beta 1a and 1b, glatiramer, teriflunomide, other immunosuppressants (ATC L04AX), monoclonal antibodies, cladribine, S1P modulators, and mitoxantrone [MED].<br>**NOT:**<br>• Interferon beta 1a and 1b, glatiramer and teriflunomide use in the previous 365 days to the cohort entry (Day 0). |
| Erythema nodosum (EN) | EN is a type of panniculitis, an inflammatory disorder affecting subcutaneous fat. It is a delayed-type hypersensitivity reaction that most often presents as erythematous tender nodules on the anterior shins. Less commonly, they affect the thighs and forearms. | The exacerbation of EN refers to a sudden and intense increase in symptoms associated with this dermatological condition. It manifests through an inflammatory response of the subcutaneous fat which leads to painful red nodules on the skin, commonly on the legs. The nodules are slightly raised and typically 2 to 5 cm in diameter. The nodules develop over several days and may follow a prodrome of fatigue, fever, malaise, arthralgias, or upper respiratory infection symptoms by one to three weeks. | Diagnosis (through diagnosis codes) of EN **AND** (at least 60 days after) (30):<br>• Identification of a general code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Acute erythema nodosum (diagnosis codes) [DIA], OR<br>• Panniculitis (diagnosis codes), including Löfgren syndrome [DIA], OR<br>• Debridement procedure (through procedure codes) [PROC], OR<br>• Initiation of one of the following drugs after a 60 days gap of no prescription or dispensing of the same drug: NSAIDs, colchicine, Dapsone, systemic corticosteroids, tetracyclines, TNF-α inhibitors, thalidomide [MED], OR.<br>• Hospitalization [H] or emergency room visit [ER] related to EN (primary diagnosis).<br>• **NOT**<br>• Acute erythema nodosum (diagnosis codes), OR Panniculitis (diagnosis codes), including Löfgren syndrome, in the previous 365 days to the cohort entry (day 0). |
| Systemic lupus erythematosus (SLE) | SLE is a chronic, relapsing, inflammatory, and often febrile multisystemic autoimmune disease of connective tissue, primarily | SLE flare-up is a measurable increase in disease activity in one or more organ systems involving new or worse clinical findings/laboratory | Diagnosis of SLE **AND** (at least 90 days after):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE]. |

| Event | Clinical definition | Flare-up definition | Flare-up algorithm* |
|---|---|---|---|
| | characterized by involvement of the skin, joints, kidneys, and serosal membranes. | measurements, that is usually accompanied by a change or an increase in the treatment, involving stronger agents or higher dosages. | • Any initiation of corticosteroids or NSAID [MED], OR<br>• Any initiation of any DMARDs (conventional nonbiologic/ synthetic, targeted synthetic, or biologic) [MED], OR<br>• Any initiation of an immunosuppressive agent (methotrexate, azathioprine, mycophenolic acid, leflunomide) [MED], OR<br>• Any initiation of a monoclonal antibody (anifrolumab, belimumab) [MED], OR<br>• Any initiation of rituximab, cclosporine, and voclosporin [MED], OR<br>• Any initiation of cyclophosphamide [MED], OR<br>• Hospitalization [H] or emergency room visit [ER] related to SLE (primary diagnosis) |
| Ulcerative colitis (UC) | UC is a type of inflammatory bowel disease (IBD) that is characterized by continuous and diffuse inflammation which is limited to the colonic mucosa and extends proximally from the rectum. | UC relapse is defined as flare-up of symptoms in a patient who is in clinical remission. Typically, these patients have rectal bleeding, increase in stool frequency and abnormal mucosa at sigmoidoscopy. The relapse is considered early if it occurs within 3 months after achieving remission with previous therapy. The pattern of relapse could be infrequent (less than or equal to 2 episodes/year), frequent (more than twice per year), or continuous (persistent symptoms of active UC without a period of remission). | Diagnosis of UC (through diagnosis codes) **AND** (at least 90 days after):<br>• Identification of a code indicating a relapse of symptoms (only for SNOMED-based codes) [FLARE], OR<br>• Rectal bleeding (through diagnosis codes) [DIA], OR<br>• Anemia (through diagnosis codes) [DIA], OR<br>• Blood transfusion or apheresis (through procedures codes) [PROC], OR<br>• Any intestinal surgery or procedure (through diagnosis codes) linked to the UC diagnosis (colectomy, proctocolectomy, restorative proctocolectomy with ileal pouch-anal anastomosis) [DIA], OR<br>• Any drug switching (as from the event definition from) [MED], OR<br>• Hospitalization [H] or emergency room visit [ER] related to UC (primary diagnosis). |

***Components of algorithms:** [MED] = based on medications; [DIA] = diagnoses of conditions; [ER] = emergency room diagnoses; [H] = hospitalization; [PROC] = procedure.

***Covariates***

All covariates were identified during the look-back period (one year) prior to the first diagnosis of the disease of interest, see Figure 1. Covariates include risk factors, comorbidities, and co-medications. Table 3 presents the comorbidities per event.

*Table 3. List of demographic characteristics and comorbidities per event and ConcePTION source table.*

| Covariate | Events | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Graves' disease** | **Hashimoto's thyroiditis** | **Polyarteritis nodose** | **Autoimmune hepatitis** | **Rheumatoid arthritis** | **Psoriatic arthritis** | **Multiple sclerosis** | **Erythema nodosum** | **Systemic lupus erythematosus** | **Ulcerative colitis** |
| Age | X | X | X | X | X | X | X | X | X | X |
| Sex | X | X | X | X | X | X | X | X | X | X |
| Immunocompromised status* | X | X | X | X | X | X | X | X | X | X |
| Pregnancy | X | X | X | X | X | X | X | X | X | X |
| Hypertension | | | | | X | X | | | X | |
| Malignancies | X | X | X | X | X | X | X | X | X | X |
| HIV | | | X | | | X | | X | | |
| Cardiocerebrovascular disease | | | | | X | X | | | | |
| Diabetes type 1 | | | | | X | X | | | | |
| Inflammatory bowel disease | | | | X | | X | | X | | |
| Infection | X | | | X | X | | | | | |
| Alcohol abuse | | | | X | X | | | | | |
| Sepsis | | | | | | | | | | |
| Chronic renal disease | | | X | | | | | | | |
| Herpes simplex | | | | X | | | | X | | |
| Influenza | | | | | | | X | | | |
| Hepatitis C | X | X | X | X | | | | X | | |
| Rheumatoid arthritis | | | | X | | | | | | |
| SLE | | | | X | | | | | | |
| Sjogren's syndrome | | X | | X | | | | | | |
| Myasthenia gravis | | X | | | | | | | | |
| Pernicious anaemia | | X | | | | | | | | |
| Autoimmune hepatitis | | X | | | | | | | | |
| Celiac disease | | X | | X | | | | | X | |
| Hepatitis B | | | X | X | | | | X | | |
| Psoriasis | | | | X | | X | | | | |
| Gout | | | | | | X | | | | |
| Atopic dermatitis | | | | | | | | | X | X |
| Non-alcoholic fatty liver | | | | | | | | | | X |
| Obesity | | | | | X | | X | | | |

* Combination of: inflammatory bowel disease, diabetes type 1, gout, AIDS, Sjogren syndrome, systemic lupus erythematosus, transplant recipient, psoriasis, psoriatic arthropathy, rheumatoid arthritis, spondylarthritis, multiple sclerosis, haematological cancer, multiple immunodeficiencies, immunosuppressants.

The following medications were assessed during the 12 months before day zero by calculating the prevalence of use during the look-back period for all study cohorts:

***Medication*** (dispensed/prescribed)

- Immunosuppressive agents (L04, H02)
- Immunostimulants (L03)
- PD-1/PD-L1 (Programmed cell death protein 1/death ligand 1) inhibitors (L01FF)
- Analgesics (N02)
- Systemic corticosteroids (H02)
- Antithrombotic agents (B01A)
- Sex hormones (G03)
- Immunosuppressants (L04, H02)
- Diabetes medications (A10A, A10B)
- Antibiotics (J01)
- Antiviral drugs (J05)
- Antimycotics (J02)
- Non-steroidal anti-inflammatory drugs (M01)
- Drug to treat mental health diseases (N05A, N06A, N06D)
- Lipid lowering drugs (C10)
- Cardiovascular meds (C01, C03, C04, C05, C07, C08, C09, B01AC, C02, C10)
- Oncologic drugs (L01, L02B, L02A)
- Anti-epileptics (N03)
- Diuretics (C03, C02L, C07B, C07C, C07D, C08G, C09BA, C09DA)
- Tumor necrosis factor (TNF) inhibitor (L04AB).

***Vaccines***

In this study, data on exposure to the following vaccines was collected to inform interruption of follow-up, alone or in combination:

- COVID-19/SARS-CoV-2
- Influenza
- Respiratory Syncitial Virus (RSV)
- Meningococcal
- Human Papillomavirus (HPV)
- Rotavirus
- Pneumococcal
- Varicella
- Mpox
- Diphtheria
- Pertussis
- Tetanus
- Poliomyelitis
- Haemophilus influenza B (HiB)
- Hepatitis B
- Measles
- Mumps
- Rubella
- Tuberculosis (BCG)
- Herpes Zoster

These vaccines were selected as they are part of the current vaccination schedule in one or more participating countries. DEAPs transformed and loaded local data on vaccinations into the VACCINE table of the ConcePTION CDM.

## 9.4 DATA SOURCES AND MEASUREMENT

This study used data from electronic health record databases that are population-based. The characteristics of each of the participating DEAPs are summarized in Table 4 and further detailed below.

*Table 4* Data provider and data sources.

| Country | Data Source (provider) | Type of data source | Estimated active population | Diagnostic coding system | Provenance of data | End date of data instance* |
|---|---|---|---|---|---|---|
| Spain (ES) | BIFAP (AEMPS) | Record linkage | 17 million | SNOMED | GP and hospital | 31-12-2023 |
| Spain (ES) | SIDIAP (IDIAP JGol) | Record linkage | 5.8 million | ICD-10/CM | GP and hospital | 31-12-2023 |
| Spain (ES) | VID (FISABIO) | Record linkage | 5.0 million | ICD-9/CM<br>ICD-10/CM | GP, hospital & outpatient specialist | 22-03-2022 |
| Italy (IT) | PEDIANET (So.Se.Te) | Family paediatrician records | 50.000 | ICD-9/CM | GP | 31-12-2022 |
| Norway (NO) | NHR (University of Oslo) | Record linkage | 5.3 million | ICPC-2<br>ICD-10/CM | Hospital & outpatient specialist | 14-01-2023 |
| United Kingdom (UK) | CPRD (Utrecht University) | GP medical records | 16 million | SNOMED | GP | 19-03-2024 |
| France (FR) | SNDS (BPE & ADERA) | Insurance claims | 6.7 million* | ICD-10 | Hospital & outpatient specialist | 07-06-2023 |

* data instance is the subset of the data source that has been ETL'ed into the CDM at a certain point in time, this instance does not necessarily contain data from all databanks in the data source, but data required for one or more studies. Data quality checks are done for each data instance.

### 9.4.1 ES: SIDIAP (CATALUNYA)

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) in Catalonia, Spain, is a primary care database set up by the Institute of Research in Primary Care (Fundació Institut Universitari D'Investigació en Atenció Primària Jordi Gol [IDIAP JGol]) and Catalan Institute of Health (Institut Català de la Salut). The database collects information from 278 primary health care centres and includes more than 5.8 million patients covered by the Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population.
SIDIAP data comprise the clinical and referral events registered by primary care health professionals (i.e., GPs, paediatricians, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. Health professionals gather this information using International Classification of Diseases, 10th Revision (ICD-10) codes, ATC codes, and structured forms designed for the collection of variables relevant to primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood urine test results. In relation to vaccines, information on all routine childhood and adult immunisations is included in addition to the antigen and the number of administered doses.
SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources databases. SIDIAP was characterised in the IMI-ADVANCE project and considered fit for purpose for vaccine coverage, benefits, and risk assessment. An algorithm to identify pregnancies has been previously used within SIDIAP. The algorithm uses diagnosis codes recorded in primary healthcare records during pregnancy and information recorded in the sexual and reproductive healthcare registries, including LMP, gestational week, expected date of delivery, actual date of delivery or termination, and pregnancy outcomes. Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research.

### 9.4.2 ES: VID (Valencia)

The Valencia health system integrated database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 48000 new-borns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and healthcare utilization data from hospital care, emergency departments, specialized care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and public health databases from the population screening programmers. All electronic health systems in the VID use the ICD-9-CM and the ICD-10-CM. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed

by all the databases from 2008 to date. Information on PCR test results as well as serological/antibody tests results for the whole population of the Valencia region is available and linkable from the Microbiological Surveillance Network (RedMIVA). The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) is Data Access Provider for Valencia Integrated Databases (VID).

### 9.4.3 ES: BIFAP (Spain, several regions)

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito público), a computerized database of medical records of primary care is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). Information collected by primary care practices (PCPs) includes administrative, socio-demographic, lifestyle, and other general data, clinical diagnosis and health problems, results of diagnostic procedures, interventions, and prescriptions/dispensations. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2, ICD-9 and SNOMEDCT system, and a variable proportion of clinical information is registered in *medical notes* in free text fields in the EMR. Additionally, information on hospital discharge diagnoses coded in ICD-10 terminology is linked to patients included in BIFAP for a subset of periods and regions participating in the database. All information on prescriptions of medicines by the PCPs is incorporated and linked by the PCPs to a health problem (episode of care), and information on the dispensation of medicines at pharmacies is extracted from the e-prescription system that is widely implemented in Spain.
The project started in 2001 and the current complete version of the database with information until December 2020 includes clinical information of 14,810 PCPs and paediatricians. Nine participant country regions send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from around 20 million (17 active population) patients representing 92% of all patients of those regions participating in the database, and 32% of the Spanish population. Mean duration of follow-up in the database is 9 years. From several regions, hospitalization data can be linked, this subpopulation is called BIFAP-HOSP-PC.

### 9.4.4 IT: Pedianet

Pedianet is a national population database that contains anonymous patient-level data of more than 500,000 children since 2004, corresponding to around 4% of the annual paediatric population who received healthcare from family paediatricians (FPs) in Italy who were part of the PEDIANET network.
The network links FPs distributed throughout several Italian regions designated by the Italian NHS, including Friuli-Venezia Giulia, Liguria, Lombardia, Piemonte, Veneto, Lazio, Marche, Toscana, Abruzzo, Campania, Sardegna, and Sicilia, and who use the same software (Junior Bit®) (Padova, Italy) in their professional practice.
According to the Italian NHS, each child is assigned to a FP, who is the primary referral for health-related matters. In Italy, there is a tax-funded public healthcare system with universal access, and patients do not incur direct costs related to primary care visits. The Pedianet database captures several types of patient-level information, including the reason for accessing healthcare, health status, demographic data, diagnosis, and clinical symptoms (free text or ICD-9-CM codes), drugs (Anatomical-Therapeutical-Chemical codes), specialist appointments, diagnostic procedures, hospital or emergency room (ER) admissions, growth parameters, and clinical outcome data. Informed consent is required

from children's parents to enter the data in the database. The data collected from the child's parents/tutors by paediatricians enters the dedicated cloud already encrypted and anonymised. Pedianet researchers do not know the process to anonymise the data and cannot know the owner of the data in any way.

### 9.4.5 NO: Norwegian national linked registers AT UIO (NHR)

The core data that the University of Oslo (UiO) has access to are the health care administrative data banks of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist healthcare services. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. The Norwegian data sources, in this project are the national, mandatory Norwegian Surveillance System for Communicable Diseases (MSIS), which was linked to five national health registries, i.e. the Medical Birth Registry, the National Patient Register, Norway Control and Payment of Health Reimbursement, the Norwegian Immunisation Registry, and the National Prescription Registry. Information about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/. In this project, University of Oslo is the DEAP for Norwegian national registry data. Their current Norwegian health registry data was used, capitalizing on the existing ETL's and quality checked data instance. In specific, UiO has contributed with ETL'd data on all residents in Norway between 1.1.2017- 31.12.2022, with historical data on these individuals back to 2010. Consequently, we have not been able to provide analysis as a near real-time analysis.

### 9.4.6 UK: Clinical Practice Research Database (CPRD-AURUM)

The Clinical Practice Research Database (CPRD) from the UK collates the computerised medical records of GPs in the UK who act as the gatekeepers of health care and maintain patients' life-long electronic health records. Accordingly, GPs are responsible for primary health care and specialist referrals, and they also store information about specialist referrals and hospitalisations. General practitioners act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Most of the data is coded using Read or SNOMED codes. Data validation with original records (specialist letters) is also available. The population in the data bank is generalisable to the UK population based on age, sex, socioeconomic class, and national geographic coverage CPRD Aurum versions is used. There are currently approximately 59 million individuals (acceptable for research purposes) -17 millions of whom are active (ie, still alive and registered with the GP practice)- in over 2,000 primary care practices (https://cprd.com/Data). Data include demographics, all GP/health care professional consultations (e.g., phone calls, letters, e- mails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and Read/SNOMED

codes), hospital clinic summary, preventive treatment and immunisations, and death (date and cause). For a proportion of the CPRD panel practices (> 80%), the GPs have agreed to permit the CPRD to link at the patient level to HES data. The CPRD is listed under the ENCePP resources database, and access has been provided by University Utrecht).

### 9.4.7 FR: *Système National des Données de Santé* (SNDS)

The *Système National des Données de Santé* (SNDS) is the French nationwide healthcare database. It currently covers the overall French population (about 67 million persons) from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. Using a unique pseudonymized identifier, the SNDS merges all reimbursed outpatient claims from all French health care insurance schemes (SNIIRAM database), hospital-discharge summaries from French public and private hospitals (PMSI database), and the national death registry. In this study, SNDS has contributed with a random sample of 10% of the database population. SNDS data are available since 2006 and contains information on:

- General characteristics: gender, year of birth, area of residence, deprivation index, etc.
- Death: month, year, and cause.
- Long-term disease registration associated with an ICD-10 diagnostic code.
- Outpatient reimbursed healthcare expenditures with dates and codes (ICD-10) (but not the medical indication nor result): visits, medical procedures, nursing acts, physiotherapy, lab tests, dispensed drugs and medical devices, etc. For each expenditure, associated costs, prescriber and caregiver information (specialty, private/public practice) and the corresponding dates are provided.
- Inpatient details: primary, related and associated ICD-10 diagnostic codes resulting from hospital discharge summaries with the date and duration of the hospital stay, the performed medical procedures (but no results), lab tests (but no results) and the related costs. Drugs included in the diagnosis related group cost are not captured. However, expensive drugs (i.e., the one charged in addition to the group cost) are.

Outpatient data (SNIIRAM) are uploaded to the SNDS throughout the year. It is admitted that a lag of around 6 months is required to catch 90% of the dispensing. Inpatient data (PMSI) are uploaded in one time, at the end of the following year. Hence, we consider that complete SNDS data of year Y are available in January of the year Y+2.

SNDS access is regulated: each study involving the human person with or without data extraction from the SNDS needs approval from the *Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* (CESREES) in charge of assessing scientific quality of the project, and authorization from the *Commission Nationale de l'Informatique et des Libertés* (CNIL) which is the French data protection authority, and then an agreement with the SNDS data holder (CNAM) for data extraction.

## 9.5 BIAS

Not all data sources capture the same type of information which impact on the ability to identify chronic diseases and their flares. Because of the need to capture both GP and hospital diagnoses we included data sources with different types of databanks. Vocabularies differ between ICD-9CM, ICD10-CM, and SNOMED, with different levels of granularity, which means that not all of the specific diseases can be identified. Furthermore, as described in Deliverable D2, the data sources used available data instances and some information was not extracted.

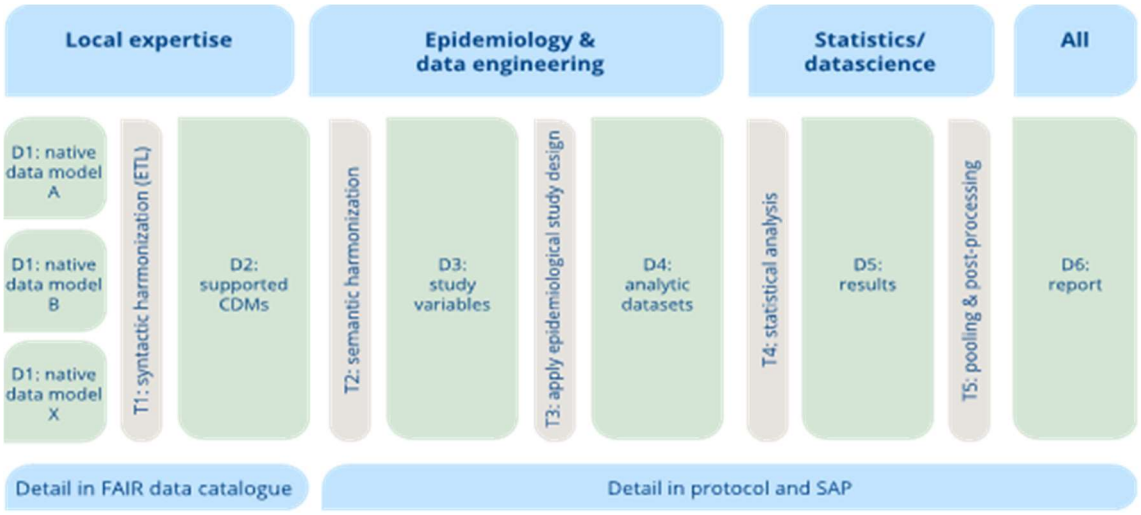
## 9.6 STUDY SIZE

This study included all subjects eligible in the data sources that could be utilized.

## 9.7 DATA TRANSFORMATION

This study was conducted in a distributed manner using the UMCU and VAC4EU tools, procedures, and pipelines. This pipeline can be viewed from a programming perspective (see Figure 2) or from a tool perspective (Figure 3). Figure 2 specifies the datasets (D) and transformation processes (T); programming follows this pipeline, with the involvement of different types of experts.

*Figure 2. Data Management from the data transformation perspective.*




***D1: Original data can be in any native format***

The RWD-RWE pipeline used by VAC4EU, and EU PE&PV starts with data banks that are controlled by the DAP, these can be in any format. This stays local. The ETL design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

***T1: Syntactic harmonisation (ETL)***

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the requested CDM. To harmonise the structure

of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (21):

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded to the FAIR data catalogue (Molgenis).

***D2: Common data model***

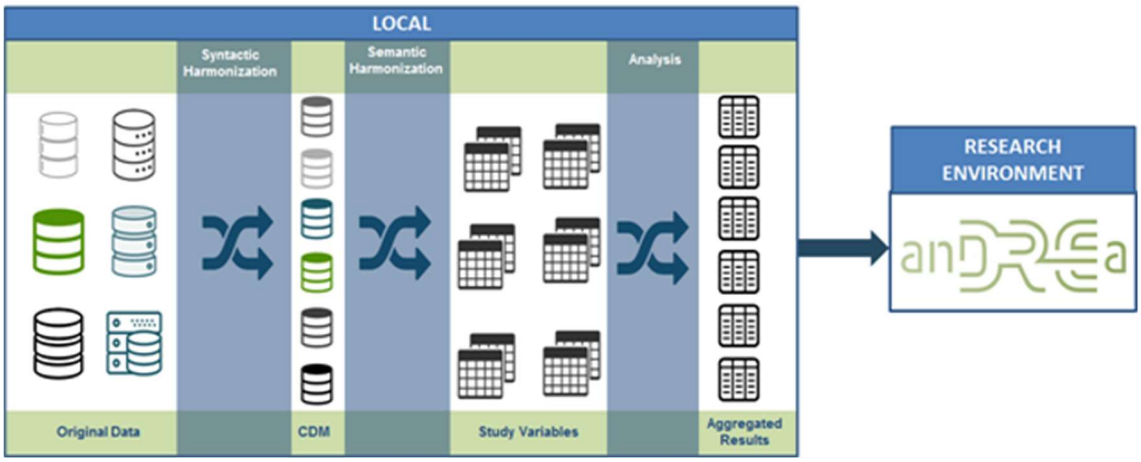
For this project, the CDM (D2) is the ConcePTION common data model (CDM). The CDM version that is used is v2.2, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes have either ICD9/10/ICPC/SNOMED values).

***T2: Semantic harmonisation***

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more **phenotype algorithms** are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP-specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable (31).

*Figure 3. Data management from a systems and location perspective*



***D3: Study variables***
D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or an episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

***T3: application of epidemiological design***
In the T3 step, epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs have been implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community.

***D4: Analytical data set***
D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

***T4: Statistical analysis***
This step in the data transformation pipeline produces statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This has been conducted using R.

***D5: Results***
D5 is the set of estimands, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE). The DRE is made available through UMCU.
The aggregated results produced by these scripts at the DEAPs site are uploaded to the UMCU DRE for post-processing, pooling, and visualization (see **Figure 3**). The DRE is a cloud-based, globally available research environment where data are stored and organized securely and where researchers can collaborate. The DRE applies double authentication where researchers can collaborate using data that is stored and organised securely. UMC Utrecht is responsible for data processing and data security.
All researchers who need access to the DRE are granted access to study-specific secure workspaces by UMCU. Access to the workspaces is possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.
The uploading of files is possible for all researchers with access to the workspace within the DRE. Downloading of files is possible only after requesting and receiving permission from a workspace member with an "owner" role, who is a UMCU team member.

***T5: Post-processing/pooling***
In this step, the result from different DEAPs is pooled and converted into tables and figures for reporting.

***Scripting and deployment***

The analytical R scripts (T2-T4 steps) are produced on VAC4EU GitHub for version control. Links to the latest script was distributed to DEAPs for local deployment. Any issues can be notified on the private GitHub, and the data engineers who are responsible for the R code worked with the local partners to resolve issues if they occur. After the final report is accepted the script will be made publicly available through GitHub (https://github.com/VAC4EU/ROC18_Objective_2) and get a digital object identifier through Zenodo.

## 9.8 STATISTICAL METHODS

All analyses were conducted using R version R-4.03 or higher (Foundation for Statistical Computing, Vienna Austria).

***Descriptive analyses***
Study attrition, description of cohorts' characteristics, and prevalence of covariates at first diagnosis are presented.

***Incidence rates and cumulative risk***
Incidence rates of flares per 1,000 PY were calculated using the number of flares in the numerator (requiring a lag time of at least 90 days (except 30 days for AIH and 60 days for EN), between repeated events to avoid misclassification due to repeated visits for a same event). Upon the occurrence of the first flare event, follow-up time was not censored, thus recurrence of a new flare after a new gap of 30, 60 or 90 days (depending on the disease) is allowed. Kaplan-Meier analyses were conducted to calculate the cumulative incidence (incidence proportion) of a first flare at 6- and 12-months after the start of follow-up. To estimate the cumulative incidence, follow-up was censored upon the earliest of a vaccination, a flare, or the end of follow-up.
Additionally, incidence rates of flares of the 10 selected autoimmune diseases were calculated in pregnant persons.

***Component analysis***
For each auto-immune condition of interest, the component strategy was applied to describe the contribution and data diversity (32) of each component of the flare identification algorithm in a data source-specific manner. We measured the number of flare cases identified and the cumulative incidence of each "component algorithm" in one study year. The combination of two or more "component algorithms" (situation named "composite algorithms") was also assessed. Incidence rates of an event of interest that are obtained from the application of the same component or composite algorithm were compared across different data sources, thus facilitating results benchmarking. The extent of the contribution of different components and composite algorithms to the observed flare rate within the same data source was quantified by describing the flare rate corresponding to the intersection of two distinct components/composite algorithms (e.g. Algorithm A "AND" Algorithm B) along with the unique contribution of each of the two component/composite algorithm (e.g. Algorithm A "AND NOT" Algorithm B). This "*component algorithm strategy"* assessed the impact of different components of the data source-specific flare-finding algorithms to the identification of flare cases. The proposed components of flare-finding algorithms were defined according to the event that prompted data recording (e.g dispensing of a drug in a community pharmacy, visit with a general practitioner) and the medical concept corresponding to the selected records (e.g. drug that are used to treat disease flare, a diagnosis of the autoimmune disease of interest).

Notably, the component algorithms possibly used for the identification a disease flare were classified as follow:
- a primary care drug prescription or a drug dispensing in a community pharmacy of a medication used to treat disease flare (MED),
- a diagnoses of conditions considered as a proxy of the autoimmune disease of interest recorded during any mediacal encounter (DIA),
- a diagnosis of the autoimmune disease of interest recorded during an emergency room visit (ER),
- a diagnosis of the autoimmune disease of interest recorded during a hospitalization (only primary diagnosis) (H),
- a medical procedures considered as a proxy of disease flare (PROC),
- a diagnosis of symptom relapse recorded during a medical encounter (FLARE)
As an example, the flare of multiple sclerosis (MS) (see section 10.5.5.1) was identified in each participating data source using at least one of the following components: i)"a general code indicating a relapse of symptoms" [FLARE], or ii) "any hospitalization [H] or emergency room visit [ER] due to MS as primary diagnosis", or iii) "any switch or addition of specific drugs for MS" [MED]. Using each component of the MS flare identification algorithm may result in a different flare rate depending on the data source, possibly due to differences in the underlying data source-specific characteristics (e.g., healthcare system organization and policies) and/or the available data meanings (e.g., different record prompts and/or healthcare settings of data collection) (33).

## 9.9 QUALITY CONTROL

Rigorous quality-control (QC) procedures were used. Data transformation into the ConcePTION CDM was conducted by each subcontracted research partner in its associated database, using the processes described in the following sections (see below), each of these steps is fully transparent and signed of/reviewed by local and central teams.
Standard operating procedures or internal process guidance available at each research centre was used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

***Quality of protocol, reports and manuscript***
All these products were reviewed by the entire consortium with many domain experts, using version control on SharePoint.

***Quality of data checks***
Data partners were asked to provide INSIGHT data quality checks (34) outputs for level 1 (completeness) and 2 (consistency) (or any EMA quality framework checks when available); level 3 is checking for study variables and assess whether data are fit for purpose. Generic open-source data quality check scripts are publicly available on the UMCU-RWE GitHub repository.[1] [2] [3] [4]

[1] https://github.com/UMC-Utrecht-RWE/ConcePTION-INSIGHT-Level1
[2] https://github.com/UMC-Utrecht-RWE/ConcePTION-INSIGHT-Level1b
[3] https://github.com/UMC-Utrecht-RWE/ConcePTION-INSIGHT-Level2
[4] https://github.com/UMC-Utrecht-RWE/ConcePTION-INSIGHT-Level3

### Level 1 - Data completeness

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspelling and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats
- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

### Level 2 - Data logic/consistency

Real data is not random but follow certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth
- Event dates after date of death
- Event dates out of observation periods
- Subjects having an observation but not present in the PERSONS table
- Observations associated with a visit id and occurred before/after the visit start/end date
- Subjects younger than 12 years old reported as parents
- Age at the observation period older than 115 years old

### Level 3

Level 3 checks review patterns of study variables over time, age within and between data sources. We have used 7 modules, which may be used depending on the study variables.

- Source and study population.
- Medicines
- Vaccines
- Diagnoses
- Pregnancy
- Populations of interest.
- Health-seeking behaviour and lifestyle factors.

***General approach to quality of R-coding***

Data Management follows standard operating procedures. R programs were made available by UMCU (INSIGHT data quality checks) and ARS. ARS has created clear documentation (graphical and in Excel spreadsheet) of the data management steps, beginning with describing the required variables from the CDM and each of the subsequent transformation steps and intermittent data tables.

*Coding conventions (process quality)*

VAC4EU GitHub (and the underlying GitHub version control system) was used to collaborate with multiple parties. At its core, GitHub tracks all changes and shows which, when, who and why changes were made. In the chain of events, any previous state can be recovered easily. Regarding proposed changes or potential bugs, GitHub provides a platform to discuss details. Using GitHub Actions, standard workflows have been defined and executed after a submitted change. An example is executing unit tests to ensure that scripts are correct.
The main coordinator of the GitHub is VAC4EU who creates a repository for the study and provides the 'main' functions to be used in each study:

- A readme file is initialized with relevant information about the scripts.
- For each study, a 'branch' is created in which scripts are tailored to the respective study.
- After each version update, the coordinator requests from all teams to incorporate the changes using 'merge'. One responsible from each team is appointed and allowed access to the repository. In case the main scripts contain an error, the 'issues' functionality is used to report the bug. If possible, a bug fix can be proposed by creating a 'pull request'. The `issues` platform also provides a means to ask for further clarification regarding new versions.

We have used one set of standard conventions for all parties to facilitate collaboration and minimize bugs in scripts. Coding conventions are categorized into three parts:

- Notation (e.g., name scripts, functions, and objects).
- Syntax (e.g., spacing, braces, indentation)
- Documentation (e.g., writing comments, dividing code into sections)

Script names are informative, where words are separated with an underscore or a hyphen. For scripts that are executed sequentially, the names are prefixed with numbers that indicate the order. For naming functions and objects, we suggest adopting the "snake style", where words are separated with an underscore. For syntax rules, we have implemented the tidy verse style guide found at https://style.tidyverse.org/. To facilitate implementing these rules, we have used the 'formatR' R package. This package automatically restyles R code to adhere to these rules. For documentation, comments that explain each part of the code have been provided. Each script file starta with a title, author, date, and version number. Comments are placed to describe functions and objects.
Scripts have been private during development and will be made public though the VAC4EU Github and Zenodo upon acceptance of the final report.

### *Standard/bespoke analyses script creation, testing and release*

Study scripts connect and package functions using a structured design and follow the statistical analysis plan. Study scripts have been created in 4 steps:

1. Defining a map of the script, which includes specification of the folder structure, data model, graphical representation of the steps, use of functions, allocation of responsibilities and timelines, plus review schedules.
2. Programming of the code by a programmer plus statistician. Test with code profiler to monitor bottlenecks in the code.
3. Test script on one real data partner before making it available for all the DAPS.
4. Take the script into deployment.

For each update, these steps are repeated.

***Quality of study conduct***

This study was conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018). All partners and principal investigators have experience in conducting pharmacovigilance/pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology or pharmacovigilance. Utrecht University and University Medical Center Utrecht (data management), and Teamit (project management) are working according to a quality management system based on ISO 9001 principles and are certified.

All partners are ENCePP centers and the majority are members of VAC4EU, a network, registered in the HMA-EMA Catalogues.

The quality management system is system and process-oriented and based on continuous improvement. The system is based upon standard operating procedures implemented throughout the divisions with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, RECORD-PE, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management. Practice as well as national and international guidelines and legislation concerning data-handling and privacy issues.

# 10 RESULTS

## 10.1 AUTOIMMUNE HEPATITIS (AIH)

### 10.1.1 Attrition of study population

Application of exclusion criteria resulted in 2954 subjects with new AIH identified in BIFAP, with 95.8% (n=2830) starting the follow-up after 90 days from the first AIH diagnosis. In VID, 1205 subjects entered the AIH cohort, and 95.5% (n=1,151) of them started the follow up. In SIDIAP, 1935 subjects entered the AIH cohort, and 96.8% (n=1874) of them started the follow up. In NHR, 1520 subjects entered the AIH cohort, and 97.1% (n=1476) started the follow up. In CPRD, 3276 subjects entered the AIH cohort, 98.2% (n=3219) of them started the follow up. In the French database SNDS, 640 AIH patients became part of the study cohort, 92.2% (n=590) of them started the follow-up. Finally, in the Italian PEDIANET database (pediatric population), there were no AIH cases identified. See Table 5 below.

*Table 5. Attrition table for the AIH cohort.*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET -IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326* | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry (inclusion) | 3,645 | 4,419 | 2,118 | 0 | 2,204 | 792 | 2,860 |
| Disease codes found during lookback | 691 | 1,143 | 913 | 0 | 269 | 152 | 1,340 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Autoimmune hepatitis | 2,954 | 3,276 | 1,205 | NA | 1,935 | 640 | 1,520 |
| Persons dying before the start of follow-up | 63 | 14 | 20 | 0 | 31 | 23 | 11 |
| Persons leaving alive the cohort before | 61 | 43 | 34 | 0 | 30 | 27 | 33 |

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| starting the follow-up (censoring) | | | | | | | |
| Persons entering follow-up | 2,830 | 3,219 | 1,151 | NA | 1,874 | 590 | 1,476 |

*BIFAP-ES contributed to this study with a subset of linked PC-hospital data only. It leaves 48.4% of the data instance population (PC only) out of the study population.
NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.1.2 Characteristics of the study cohort

The total study population who started the follow up 90 days after diagnosis, across databases, comprised 11,140 persons. The total follow-up time ranged from 1,133 PY in SNDS to 10,446 PY in CPRD. On average, 71% of the cohort population were females. The male-to-female sex ratio in AIH incident cases across databases was 40 males to every 100 females. The median age (interquartile range 50) was between 58- to 60-year-old across data sources. These figures are compatible with demographic knowledge about AIH in the general population (35). The percentage of people with at least 3 vaccinations ranged from 9.3% in CPRD to 65.1% in NHR. See
Table 6.

*Table 6. Characteristics of the AIH study cohort population.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 2,954 | 3,276 | 1,205 | 0 | 1,935 | 640 | 1,520 |
| Female (n/%) | 2,117 (71.7%) | 2,346 (71.6%) | 895 (74.3%) | NA | 1,363 (70.4%) | 441 (68.9%) | 1,069 (70.3%) |
| Male (n/%) | 837 (28.3%) | 930 (28.4%) | 310 (25.7%) | NA | 572 (29.6%) | 199 (31.1%) | 451 (29.7%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 49 | 46 | 47 | NA | 48 | 42 | 42 |
| Age in year (IQR): PCT 50 | 60.0 | 60.0 | 58.0 | NA | 60.0 | 58.5 | 58.0 |
| Age in year (IQR): PCT 75 | 72 | 71 | 70 | NA | 72 | 71 | 69 |
| Age in categories (n/%): < 18 | 127 (4.3%) | 166 (5.1%) | 32 (2.7%) | NA | 77 (4%) | 45 (7%) | 88 (5.8%) |
| Age in categories (n/%): 18-59 | 1,291 (43.7%) | 1,407 (42.9%) | 604 (50.1%) | NA | 858 (44.3%) | 282 (44.1%) | 726 (47.8%) |
| Age in categories (n/%): > 60 | 1,536 (52%) | 1,703 (52%) | 569 (47.2%) | NA% | 1,000 (51.7%) | 313 (48.9%) | 706 (46.4%) |
| Number of persons who started the follow-up | 2,830 (95.8%) | 3,219 (98.3%) | 1,151 (95.5%) | NA% | 1,874 (96.8%) | 590 (92.2%) | 1,476 (97.1%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 8,052 | 10,446 | 1,907 | NA | 5,420 | 1,133 | 4,188 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 1 | NA | 3 | 1 | 4 |
| Number of people with vaccinations (n/%): 0 | 715 (24.2%) | 2,391 (73%) | 505 (41.9%) | NA | 544 (28.1%) | 254 (39.7%) | 205 (13.5%) |
| Number of people with vaccinations (n/%): 1 | 277 (9.4%) | 335 (10.2%) | 256 (21.2%) | NA | 166 (8.6%) | 115 (18%) | 128 (8.4%) |
| Number of people with vaccinations (n/%): 2 | 314 (10.6%) | 188 (5.7%) | 173 (14.4%) | NA | 212 (11%) | 89 (13.9%) | 154 (10.1%) |
| Number of people with vaccinations (n/%): 3 or more | 1,524 (51.6%) | 305 (9.3%) | 217 (18%) | NA | 952 (49.2%) | 132 (20.6%) | 989 (65.1%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 7 below describes comorbidities for all data sources. PEDIANET did not have any person in the AIH cohort. The AIH population with a code or drug implying an immunocompromised status during the look-back period ranged from 19% (BIFAP) to 40% (VID) across data sources. Cancer diagnosis was identified in 6.1% to 8.9% of the cohort population. Prevalence of a previous infection during the look-back period ranged between 35.4% (NHR) to 57.7% (SNDS). SNDS reports the highest prevalence of medicines use in most of the selected therapeutic groups, except for systemic corticosteroids, mental health diseases drugs, lipid lowering drugs. NSAIDs and diuretics were not ETL´ed in the data instance used in this study. . Prevalence of antibiotic use in AIH patients was between 30.8 (NHR) and 53.9% (SNDS) across databases.

*Table 7. Comorbidities in the study cohort with AIH.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 2,954 | 3,276 | 1,205 | 0 | 1,935 | 640 | 1,520 |
| Immunocompromise status (n/%) | 557 (18.9%) | 855 (26.1%) | 481 (39.9%) | NA | 590 (30.5%) | 228 (35.6%) | 499 (32.8%) |
| Malignancy (n/%) | 211 (7.1%) | 199 (6.1%) | 89 (7.4%) | NA | 167 (8.6%) | 66 (10.3%) | 135 (8.9%) |
| Inflammatory bowel disease (n/%) | 21 (0.7%) | 52 (1.6%) | 23 (1.9%) | NA | 16 (0.8%) | 17 (2.7%) | 125 (8.2%) |
| Infection (n/%) | 1,090 (36.9%) | 1,331 (40.6%) | 561 (46.6%) | NA | 737 (38.1%) | 369 (57.7%) | 538 (35.4%) |
| Alcohol abuse (n/%) | 86 (2.9%) | 22 (0.7%) | 32 (2.7%) | NA | 40 (2.1%) | 26 (4.1%) | 38 (2.5%) |
| Herpes simplex (n/%) | 8 (0.3%) | 0 (0%) | 7 (0.6%) | NA | 16 (0.8%) | < 5 | < 5 |
| Hepatitis C (n/%) | 11 (0.4%) | 12 (0.4%) | 9 (0.7%) | NA | 11 (0.6%) | < 5 | 5 (0.3%) |
| Rheumatoid arthritis (n/%) | 11 (0.4%) | 33 (1%) | 34 (2.8%) | NA | 18 (0.9%) | < 5 | 65 (4.3%) |
| SLE (n/%) | 24 (0.8%) | 31 (0.9%) | 31 (2.6%) | NA | 20 (1%) | 7 (1.1%) | 18 (1.2%) |
| Sjogren's syndrome (n/%) | 18 (0.6%) | 19 (0.6%) | 17 (1.4%) | NA | 28 (1.4%) | < 5 | 38 (2.5%) |
| Celiac disease (n/%) | 10 (0.3%) | 24 (0.7%) | 21 (1.7%) | NA | 15 (0.8%) | 0 (0%) | 12 (0.8%) |
| Hepatitis B (n/%) | 6 (0.2%) | 6 (0.2%) | < 5 | NA | 5 (0.3%) | < 5 | 5 (0.3%) |
| Psoriasis (n/%) | 22 (0.7%) | 26 (0.8%) | 22 (1.8%) | NA | 15 (0.8%) | < 5 | 39 (2.6%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 822 (27.8%) | 1,321 (40.3%) | 554 (46%) | NA | 726 (37.5%) | 349 (54.5%) | 802 (52.8%) |
| Immunostimulants (n/%) | 0 (0%) | 0 (0%) | 7 (0.6%) | NA | 0 (0%) | < 5 | < 5 |
| Analgesics (n/%) | 1,265 (42.8%) | 895 (27.3%) | 624 (51.8%) | NA | 890 (46%) | 465 (72.7%) | 357 (23.5%) |
| Systemic corticosteroids (n/%) | 608 (20.6%) | 946 (28.9%) | 383 (31.8%) | NA | 486 (25.1%) | 250 (39.1%) | 734 (48.3%) |
| Antithrombotic agents (n/%) | 627 (21.2%) | 607 (18.5%) | 233 (19.3%) | NA | 398 (20.6%) | 173 (27%) | 382 (25.1%) |
| Sex hormones (n/%) | 70 (2.4%) | 356 (10.9%) | 32 (2.7%) | NA | 32 (1.7%) | 74 (11.6%) | 0 (0%) |
| Diabetes medications (n/%) | 376 (12.7%) | 387 (11.8%) | 176 (14.6%) | NA | 299 (15.5%) | 98 (15.3%) | 182 (12%) |

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Antibiotics (n/%) | 936 (31.7%) | 1,270 (38.8%) | 524 (43.5%) | NA | 647 (33.4%) | 345 (53.9%) | 468 (30.8%) |
| Antiviral drugs (n/%) | 36 (1.2%) | 67 (2%) | 39 (3.2%) | NA | 30 (1.6%) | 40 (6.2%) | 31 (2%) |
| Antimycotics (n/%) | 28 (0.9%) | 56 (1.7%) | 0 (0%) | NA | 18 (0.9%) | 34 (5.3%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 688 (23.3%) | 291 (8.9%) | 357 (29.6%) | NA | 469 (24.2%) | NA | 304 (20%) |
| Drug to treat mental health diseases (n/%) | 584 (19.8%) | 812 (24.8%) | 231 (19.2%) | NA | 368 (19%) | 87 (13.6%) | 192 (12.6%) |
| Lipid lowering drugs (n/%) | 747 (25.3%) | 937 (28.6%) | 312 (25.9%) | NA | 468 (24.2%) | 134 (20.9%) | 421 (27.7%) |
| Cardiovascular medication (n/%) | 1,367 (46.3%) | 1,590 (48.5%) | 590 (49%) | NA | 950 (49.1%) | 347 (54.2%) | 358 (23.6%) |
| Oncologic drugs (n/%) | 54 (1.8%) | 108 (3.3%) | 47 (3.9%) | NA | 47 (2.4%) | 46 (7.2%) | 28 (1.8%) |
| Anti-epileptics (n/%) | 189 (6.4%) | 60 (1.8%) | 93 (7.7%) | NA | 155 (8%) | 48 (7.5%) | 65 (4.3%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | 0 (0%) | NA | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 7 (0.2%) | 13 (1.1%) | NA | 0 (0%) | 12 (1.9%) | 29 (1.9%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.1.3 IRs of AIH flares

#### 10.1.3.1 IRs of AIH flares in the general population

The number of individuals who developed a first AIH flare episode in BIFAP was 1,349, leading to an IR of 401.5 per 1000 PY (CI95% 380.4-423.5), whereas in CPRD was 1193, leading to an IR of 179.5 per 1000 PY (CI 95% 169.5-190). In VID, 482 persons developed a first flare-up, leading to an IR of 459.4 per 1,000 PY (CI 95% 419.3-502.3). In SIDIAP, 955 patients developed a first flare-up episode accounting for an IR of 412.6 (CI 95% 386.9-439.7). In SNDS, 201 subjects flared-up, leading to an IR of first flare-up episode of 307.3 per 1,000 PY (CI 95% 266.3-352.8). Finally, in NHR, 659 patients developed a first flare up, leading to an IR of 384.6 per 1000 PY (CI 95% 355.8-415.2). IRs of second flare-up episodes decreased in all data sources to 236.3 cases per 1000 PY less in BIFAP, 123.7 cases per 1000 PY in CPRD, 234.2 per 1,000 PY in VID, 227.8 per 1000 PY in SIDIAP, 166.2 per 1,000 PY in SNDS, and 215.8 per 1,000 PY in NHR. On average, IRs of the second flare episode were 156.8 per 1,000 PY, meaning an average decrease of more than 60% in relation to the first flare episode. The IR of the third flare-up episode decreased in relation to the second flare in BIFAP (80.9 per 1000 PY), CPRD (41.9 per 1000 PY), SIDIAP (124.1 per 1000 PY) and NHR (157 per 1,000 PY). On the contrary, it increased in VID (321.9 per 1,000 PY) and in SNDS (446.4 per 1,000 PY). In SNDS, the IR of the third flare episode was higher than the rate of the first flare up, although confidence intervals overlapped. See Table 8 below.

*Table 8. Background incidence rate of first, second, and third flare in the AIH cohort per 1,000 person-years (95% confidence interval).*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 2,954 | 3,276 | 1,205 | 0 | 1,935 | 640 | 1,520 |

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Number of persons who started the follow-up | 2,809 | 3,214 | 1,140 | NA | 1,870 | 584 | 1,472 |
| Number of persons who develop a first flare-up episode | 1,349 | 1,193 | 482 | NA | 955 | 201 | 659 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 401.5 (380.4-423.5) | 179.5 (169.5-190) | 459.4 (419.3-502.3) | NA | 412.6 (386.9-439.7) | 307.3 (266.3-352.8) | 384.6 (355.8-415.2) |
| Number of persons still in the study 90 days after first flare | 1,304 | 1,160 | 453 | NA | 944 | 192 | 643 |
| Number of persons who develop a second flare-up episode | 341 | 159 | 96 | NA | 260 | 35 | 158 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 165.2 (148.1-183.7) | 55.8 (47.4-65.1) | 225.2 (182.4-275) | NA | 184.8 (163-208.7) | 141.1 (98.3-196.3) | 168.8 (143.5-197.2) |
| Number of persons still in the study 90 days after second flare | 327 | 155 | 89 | NA | 256 | 34 | 155 |
| Number of persons who develop a third flare-up episode | 42 | 13 | 16 | NA | 49 | 12 | 33 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 80.9 (58.3-109.4) | 41.9 (22.3-71.7) | 321.9 (184-522.8) | NA | 124.1 (91.8-164) | 446.4 (230.7-779.7) | 157 (108.1-220.5) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations)

#### 10.1.3.2 IRs of AIH flares stratified per age categories

Most of the people experiencing flares of AIH were adults ≥ 18 years old and over 60 years old. Overall, rates for all episodes were slightly higher for 0-17-year-olds, followed by 18-59 and then ≥60 age categories. The incidence of the first flare episodes was higher than the incidence of the second flare episodes for all age categories and across data sources, as shown in Table 9.

In the 0-17-year-old population, IRs for the first flare episodes ranged from 228.3 (NHR) to 493.3 (SIDIAP) per 1000 PY, while for the second flare episodes, values were between 31.4 (CPRD) to 389.1 (VID) per 1000 PY. In the 18-59-year-old population, IRs for the first flare episode span from 187.6 (CPRD) to 439.2 (SIDIAP) per 1000 PY, while for the second flare episode, values were between 61.1 (CPRD) and 238.1 (VID) per 1000 PY.

For the ≥60-year-old population, the IRs for first flare episodes were observed between 166.4 (CPRD) and 475.6 (VID) per 1000 PY, while for the second ones ranged from 53.7 (CPRD) and 200.8 (VID) per 1000 PY. People experiencing a third flare episode are <5 across all data sources for the 0-17 years-old-age category. For all adult categories, the incidence of a third flare episode is overall lower than the second episode one, except for VID in ≥60 years old and SNDS in 18-59 years old individuals, while <5 cases were counted for ≥60 years old in this latter data source.

*Table 9 Background incidence rate of first, second, and third flare in the AIH cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 62 | 65 | 16 | NA | 41 | 20 | 25 |
| Number of persons who develop a first flare-up episode | 18-59 | 620 | 515 | 233 | NA | 437 | 103 | 344 |
| Number of persons who develop a first flare-up episode | 60+ | 667 | 613 | 233 | NA | 477 | 78 | 290 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 435.3 (333.7-558) | 300.1 (231.6-382.5) | 747.7 (427.4-1214.2) | NA | 493.3 (354-669.2) | 478.3 (292.2-738.7) | 228.3 (147.7-337) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 420 (387.6-454.4) | 187.6 (171.8-204.6) | 433.1 (379.3-492.5) | NA | 439.2 (399-482.4) | 308.8 (252.1-374.5) | 432.6 (388.1-480.8) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 383 (354.5-413.3) | 166.4 (153.5-180.1) | 475.6 (416.5-540.7) | NA | 385.8 (352-422.1) | 279.8 (221.2-349.2) | 358.7 (318.6-402.4) |
| Number of persons still in the study 90 days after first flare | 0-17 | 59 | 62 | 16 | NA | 39 | 19 | 23 |
| Number of persons still in the study 90 days after first flare | 18-59 | 609 | 521 | 224 | NA | 440 | 102 | 345 |
| Number of persons still in the study 90 days after first flare | 60+ | 717 | 659 | 232 | NA | 519 | 84 | 308 |
| Number of persons who develop a second flare-up episode | 0-17 | 16 | < 5 | 5 | | 11 | 6 | 5 |
| Number of persons who develop a second flare-up episode | 18-59 | 162 | 72 | 51 | | 129 | 19 | 84 |
| Number of persons who develop a second flare-up episode | 60+ | 163 | 83 | 40 | | 120 | 10 | 69 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 192 (109.8-311.8) | 31.4 (8.6-80.5) | 389.1 (126.3-907.9) | NA | 213.5 (106.6-382) | 364.5 (133.8-793.3) | 196.5 (63.8-458.5) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 163.3 (139.1-190.5) | 61.1 (47.8-77) | 238.1 (177.3-313.1) | NA | 212.7 (177.6-252.8) | 154.5 (93-241.3) | 163.5 (130.4-202.4) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 164.9 (140.5-192.2) | 53.7 (42.7-66.5) | 200.8 (143.4-273.4) | NA | 160.2 (132.8-191.5) | 92.1 (44.2-169.4) | 173.8 (135.2-220) |
| Number of persons still in the study 90 days after second flare | 0-17 | 16 | < 5 | < 5 | | 11 | 6 | 5 |
| Number of persons still in the study 90 days after second flare | 18-59 | 159 | 70 | 48 | | 125 | 19 | 85 |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons still in the study 90 days after second flare | 60+ | 177 | 91 | 38 | | 135 | 9 | 68 |
| Number of persons who develop a third flare-up episode | 0-17 | < 5 | < 5 | 0 | | < 5 | < 5 | NR |
| Number of persons who develop a third flare-up episode | 18-59 | 17 | 7 | 7 | | 21 | 6 | NR |
| Number of persons who develop a third flare-up episode | 60+ | 21 | 5 | 9 | | 24 | < 5 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 221.6 (60.4-567.5) | 143 (3.6-796.5) | 0 (0-1212.7) | NA | 390.5 (106.4-999.9) | 1001.6 (206.6-2927.1) | 367.8 (9.3-2049.4) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 65.4 (38.1-104.8) | 54.1 (21.7-111.4) | 213.8 (85.9-440.5) | NA | 108.3 (67-165.5) | 359.3 (131.9-782.1) | 148.7 (88.1-235) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 87.1 (53.9-133.1) | 28.8 (9.4-67.2) | 646.8 (295.8-1227.9) | NA | 125.9 (80.6-187.3) | 417.3 (86.1-1219.4) | 162 (88.6-271.8) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.1.3.3 IRs of AIH flares stratified per gender

Across all data sources, the number of females experiencing a first, second, or third episode of AIH flares was higher than that of males, as shown in Table 10. This is in line with the reported evidence about AIH being a disease that mainly affects females, irrespective of age, race or ethnicity (27,36). Regarding the incidence of AIH flares cases, no major differences have been observed between females and males across data sources and first, second, and third episodes. For the first flare episode, the male population IRs per 1000 PY ranged from 185.9 (CPRD) to 425.7 (VID), while the female population values ranged from 177 (CPRD) to 471.5 (VID). For the second episode, the lower male population incidence per 1000 PY was 58 (CPRD), the highest was 225.1 (VID), and the female incidence span from 54.8 (CPRD) to 225.1 (VID). Regarding the incidence for the third episode, again the lowest values were observed in CPRD (27 for females and 80.2 per 1000 PY for males) and the highest in SNDS for females (306.6 per 1000 PY) and in VID for males (655.2 per 1000 PY).

*Table 10. Background incidence rate of first, second, and third flare in the AIH cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 994 | 848 | 364 | NA | 688 | 137 | 485 |
| Number of persons who develop a first flare-up episode | M | 355 | 345 | 118 | NA | 267 | 64 | 174 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 408.2 (383.3-434.4) | 177 (165.3-189.4) | 471.5 (424.3-522.5) | NA | 420.7 (389.9-453.4) | 283.6 (238.1-335.3) | 420.6 (384-459.7) |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 383.8 (344.9-425.8) | 185.9 (166.8-206.6) | 425.7 (352.4-509.8) | NA | 393.1 (347.4-443.2) | 374.1 (288.1-477.8) | 310.7 (266.2-360.4) |
| Number of persons still in the study 90 days after first flare | F | 965 | 825 | 344 | NA | 683 | 132 | 471 |
| Number of persons still in the study 90 days after first flare | M | 339 | 335 | 109 | NA | 261 | 60 | 172 |
| Number of persons who develop a second flare-up episode | F | 248 | 113 | 73 | | 191 | 16 | 127 |
| Number of persons who develop a second flare-up episode | M | 93 | 46 | 23 | | 69 | 19 | 31 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 157.3 (138.4-178.2) | 54.8 (45.1-65.9) | 225.1 (176.4-283) | NA | 185.7 (160.3-214) | 95.5 (54.6-155.1) | 191.4 (159.6-227.7) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 190.6 (153.9-233.6) | 58.3 (42.7-77.8) | 225.7 (143.1-338.7) | NA | 182.3 (141.8-230.7) | 235.9 (142-368.4) | 113.7 (77.3-161.4) |
| Number of persons still in the study 90 days after second flare | F | 235 | 109 | 69 | | 189 | 15 | 125 |
| Number of persons still in the study 90 days after second flare | M | 92 | 46 | 20 | | 67 | 19 | 30 |
| Number of persons who develop a third flare-up episode | F | 29 | 6 | 10 | | 35 | < 5 | 27 |
| Number of persons who develop a third flare-up episode | M | 13 | 7 | 6 | | 14 | 8 | 6 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 74.5 (49.9-107) | 27 (9.9-58.7) | 246.7 (118.3-453.6) | NA | 118.7 (82.7-165) | 306.6 (83.5-785) | 162.3 (106.9-236.1) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 100.1 (53.3-171.1) | 80.2 (32.2-165.2) | 655.2 (240.4-1426) | NA | 140 (76.6-235) | 578.2 (249.6-1139.2) | 137.1 (50.3-298.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.1.3.4 IRs of AIH flares in pregnant population

VID, SIDIAP and NHR identified pregnant women in the AIH cohort population. BIFAP-ES, CPRD, PEDIANET (adolescents up to 14 years of age) and SNDS did not run the pregnancy algorithm. Seven persons who have at least one pregnancy after the start of follow-up were identified in VID, 21 in SIDIAP, and 30 in NHR. The IRs of the first flare episode of AIH among women becoming pregnant in VID was 378.9 (CI 95% 9.6 – 2111), in SIDIAP was 577.6 (CI 95% 212-1257.2), and in NHR was 144.8 (CI 95% 17.5-523). The number of persons who developed a second and third flare episodes while pregnant were very few. See Table 11 below.

*Table 11. IR in pregnant population of first, second, and third flare in the AIH cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 7 | 21 | NA | 30 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | < 5 | 6 | NA | < 5 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 378.9 (9.6-2111) | 577.6 (212-1257.2) | NA | 144.8 (17.5-523) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | < 5 | 7 | NA | 9 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | 0 | NA | 0 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 709.2 (18-3951.5) | 0 (0-909.8) | NA | 0 (0-1131.3) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | NA | < 5 | NA | < 5 |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | NA | 0 | NA | 0 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | 0 (0-7166.8) | NA | 0 (0-2606.1) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.1.4 Six- and twelve-months cumulative incidence of the first flare episode of AIH in the general population

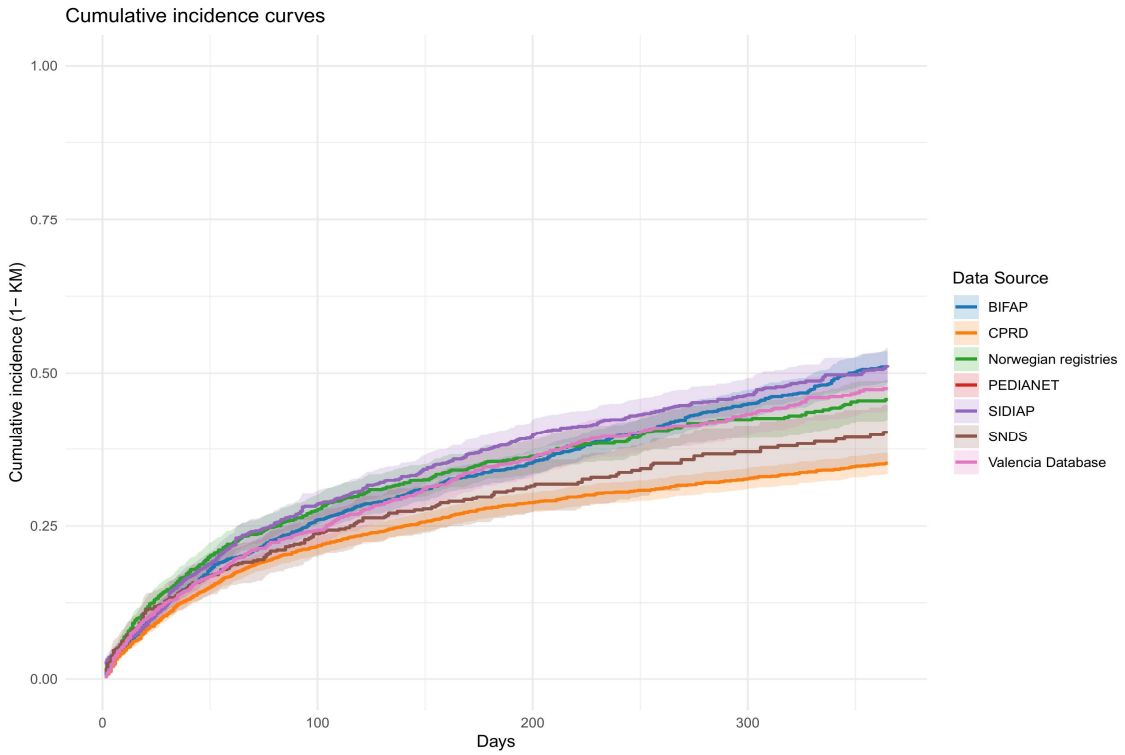
Table 12 shows the 6- and 12-months cumulative incidence of the first flare episode from AIH. The 6-month risk of a first flare in AIH patients from the start of follow-up was 34.6% for VID, 37.6% for SIDIAP, 35.5% in NHR, 33.8 in BIFAP, 27.9% in CPRD, and 29.7% for SNDS. The individual risk of AIH patients of representing a flare episode during the 1-year timespan was 51.1% in BIFAP, 35.2% in CPRD, 47.5% in VID, 51.3% in SIDIAP, 40.3% in SNDS, and 45.7% in NHR. The cumulative incidence curve is presented in Figure 4.

*Table 12. Six- and twelve-months cumulative incidence of flares of AIH (95% confidence interval).*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|
| 180 | 0.355 (0.327-0.382) | 0.346 (0.315-0.376) | 0.376 (0.351-0.4) | 0.338 (0.318-0.357) | 0.297 (0.256-0.336) | 0.279 (0.263-0.295) |
| 365 | 0.457 (0.423-0.489) | 0.475 (0.438-0.51) | 0.513 (0.484-0.541) | 0.511 (0.485-0.536) | 0.403 (0.354-0.448) | 0.352 (0.334-0.369) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 4. Cumulative incidence curve AIH.*

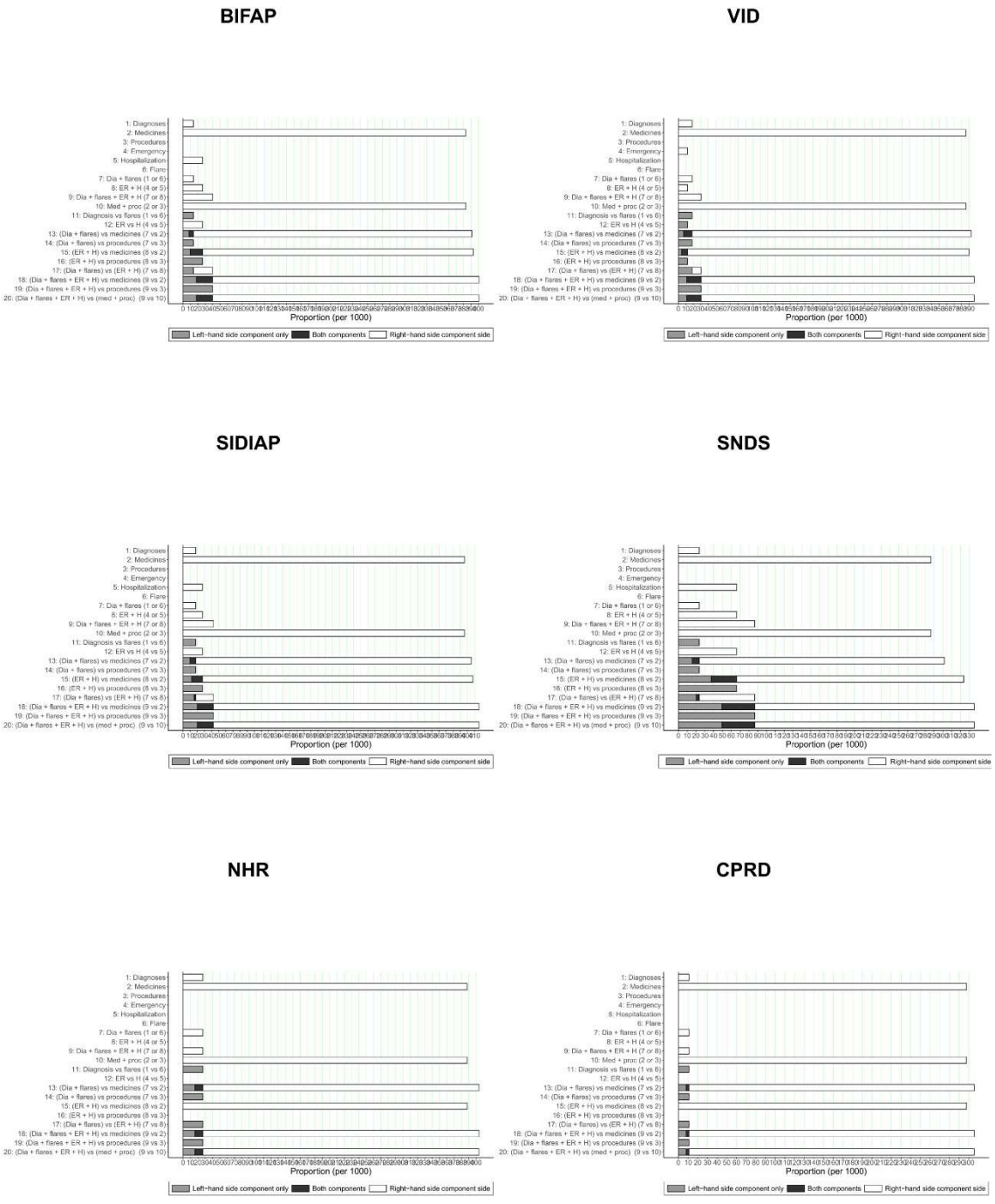



### 10.1.5 Other analyses

#### 10.1.5.1 Component analysis

Considering the components used to identify AIH flares (see Figure 5), medications (MED) accounted for the highest annual cumulative incidence of the first AIH flare across all data sources, ranging from 85.3% in SNDS to 97.4% in CPRD. The remaining cases of AIH flares were identified through diagnoses of conditions (DIA) in NHR and CRPD, DIA and hospitalization (H) in SIDIAP, BIFAP and SNDS, and DIA and emergency room diagnoses (ER) in VID. The overlapping of identified flare cases across different components (e.g., MED and DIA+ER) was low, ranging from 0.9% (CPRD) to 11.1% (SNDS).

*Figure 5. Component Analysis for AIH.*



## 10.2 ERYTHEMA NODOSUM (EN)

### 10.2.1 Attrition of study population

A relatively high number of persons had a code of EN during the study period. The application of initial and other exclusion criteria (panniculitis, including Löfgren syndrome, identified during the look-back period) to ensure incident EN, had a great impact in the study attrition. See Table 13 below. 4,204 persons entered the EN cohort in BIFAP, 25 in VID, 5 in PEDIANET, 120 in SIDIAP, 420 in SNDS and 7 in NHR. There were no cases of new EN identified in CPRD.

*Table 13. Attrition table for the EN cohort.*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326* | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 4,691 | 6,092 | 742 | 6 | 3,266 | 434 | 739 |
| Disease codes found during lookback | 478 | 270 | 197 | < 5 | 157 | 14 | 46 |
| Other criteria suggesting the disease is present during lookback | 9 | 5,822 | 520 | 0 | 2,989 | 0 | 686 |
| Total cohort of Erythema nodosum | 4,204 | NA | 25 | 5 | 120 | 420 | 7 |
| Persons dying before entrance in the follow-up | 7 | 0 | NR | 0 | < 5 | NR | 0 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 97 | 0 | NR | 0 | < 5 | NR | 0 |
| Persons entering follow-up | 4,100 | NA | 24 | 5 | 115 | 408 | 7 |

*BIFAP-ES contributed to this study with a subset of linked PC-hospital data only. It leaves 48.4% of the data instance population (PC only) out of the study population.
NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.2.2 Characteristics of the study cohort

Females accounted for 71% to 81.2% of the incident EN cohort population across databases. Median age of the cohort population ranged from 37.5-year-old in SNDS to 65-year-old in NHR. In BIFAP, 48.5% (n=2,040) of the persons who started the follow-

up received 3 or more vaccinations during follow up. In SIDIAP, from the persons who started the follow-up (n=115), 50,8% (n=61) received 3 or more vaccinations during follow-up. In SNDS, 408 persons started the follow-up, 10.2% (n=43) of them received 3 or more vaccinations. In NHR, 7 persons started the follow-up, 71.4% (n=5) received 3 or more vaccinations. Finally, from the 24 and 5 persons who started the follow-up in VID and PEDIANET, respectively, <5 persons received 3 or more vaccinations. See Table 14.

*Table 14. Characteristics of the EN cohort population.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 4,204 | 0 | 25 | 5 | 120 | 420 | 7 |
| Female (n/%) | 3413 (81.2%) | NA | 18 (72%) | < 5 | 95 (79.2%) | 298 (71%) | NR |
| Male (n/%) | 791 (18.8%) | NA | 7 (28%) | < 5 | 25 (20.8%) | 122 (29%) | NR |
| Other (n/%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | NR |
| Age in year (IQR): PCT 25 | 31.00 | NA | 35.00 | 3.00 | 40.75 | 25.75 | 37.50 |
| Age in year (IQR): PCT 50 | 45.0 | NA | 50.0 | 5.0 | 55.5 | 37.5 | 65.0 |
| Age in year (IQR): PCT 75 | 60.00 | NA | 61.00 | 5.00 | 70.25 | 52.00 | 69.00 |
| Age in categories (n/%): < 18 | 355 (8.4%) | NA | 0 (0%) | 5 (100%) | < 5 | 49 (11.7%) | < 5 |
| Age in categories (n/%): 18-59 | 2,764 (65.7%) | NA | 18 (72%) | 0 (0%) | 63 (52.5%) | 300 (71.4%) | < 5 |
| Age in categories (n/%): > 60 | 1,085 (25.8%) | NA | 7 (28%) | 0 (0%) | 53 (44.2%) | 71 (16.9%) | < 5 |
| Number of persons who started the follow-up | 4,100 (97.5%) | 0 (NA%) | 24 (96%) | 5 (100%) | 115 (95.8%) | 408 (97.1%) | 7 (100%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 14,066 | 0 | 51 | 14 | 381 | 817 | 24 |
| Number of vaccinations during follow-up (median, IQR) | 2 | NA | 0 | 0 | 3 | 0 | 4 |
| Number of people with vaccinations (n/%): 0 | 1,013 (24.1%) | NA | 13 (52%) | < 5 | 29 (24.2%) | 263 (62.6%) | < 5 |
| Number of people with vaccinations (n/%): 1 | 397 (9.4%) | 0 (NA%) | 6 (24%) | 0 (0%) | 9 (7.5%) | 51 (12.1%) | 0 (0%) |
| Number of people with vaccinations (n/%): 2 | 650 (15.5%) | NA | < 5 | 0 (0%) | 16 (13.3%) | 51 (12.1%) | < 5 |
| Number of people with vaccinations (n/%): 3 or more | 2,040 (48.5%) | NA | < 5 | < 5 | 61 (50.8%) | 43 (10.2%) | 5 (71.4%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Regarding underlying conditions, 12.7% of BIFAP population was dispensed or prescribed an immunosuppressive drug, 6.2% of the people were living with an immunocompromised status, 2.7% had a cancer diagnosis, 5.2% were assuming diabetes medications, 33.1% was assuming non-steroidal anti-inflammatory drugs, 25.3% were under cardiovascular medications, and 33.6% consumed an antibiotic during the look-back period. In SIDIAP, 25% of the population was dispensed or prescribed an immunosuppressive drug, 48.3% was assuming non-steroidal anti-inflammatory drugs, 43.3% were under cardiovascular medications, and 50% consumed an antibiotic during the look-back period. In SNDS, 43.1% of the population was dispensed or prescribed an immunosuppressive drug, 26.7% were under cardiovascular medications, and 69.8% consumed an antibiotic during the look-back period. In VID, 56% (n=14) of the

population was dispensed or prescribed an antibiotic and the same percentage was assuming non-steroidal anti-inflammatory drugs. See Table 15.

*Table 15. Comorbidities in the study cohort with EN.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 4,204 | 0 | 25 | 5 | 120 | 420 | 7 |
| Immunocompromise status (n/%) | 259 (6.2%) | 0 (0%) | < 5 | 0 (0%) | 18 (15%) | 73 (17.4%) | < 5 |
| Malignancy (n/%) | 112 (2.7%) | 0 (0%) | < 5 | 0 (0%) | 6 (5%) | 28 (6.7%) | 0 (0%) |
| HIV (n/%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 0 (0%) |
| Inflammatory bowel disease (n/%) | 69 (1.6%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 25 (6%) | 0 (0%) |
| Herpes simplex (n/%) | 22 (0.5%) | 0 (0%) | < 5 | 0 (0%) | < 5 | < 5 | 0 (0%) |
| Hepatitis C (n/%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 0 (0%) |
| Hepatitis B (n/%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 535 (12.7%) | 0 (0%) | < 5 | < 5 | 30 (25%) | 181 (43.1%) | < 5 |
| Immunostimulants (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 0 (0%) |
| Analgesics (n/%) | 1628 (38.7%) | 0 (0%) | 16 (64%) | 0 (0%) | 72 (60%) | 351 (83.6%) | < 5 |
| Systemic corticosteroids (n/%) | 456 (10.8%) | 0 (0%) | < 5 | < 5 | 28 (23.3%) | 170 (40.5%) | < 5 |
| Antithrombotic agents (n/%) | 461 (11%) | 0 (0%) | 8 (32%) | 0 (0%) | 25 (20.8%) | 73 (17.4%) | < 5 |
| Sex hormones (n/%) | 317 (7.5%) | 0 (0%) | < 5 | 0 (0%) | 6 (5%) | 107 (25.5%) | 0 (0%) |
| Diabetes medications (n/%) | 217 (5.2%) | 0 (0%) | < 5 | 0 (0%) | 14 (11.7%) | 19 (4.5%) | 0 (0%) |
| Antibiotics (n/%) | 1413 (33.6%) | 0 (0%) | 14 (56%) | < 5 | 60 (50%) | 293 (69.8%) | < 5 |
| Antiviral drugs (n/%) | 56 (1.3%) | 0 (0%) | < 5 | 0 (0%) | 0 (0%) | 25 (6%) | 0 (0%) |
| Antimycotics (n/%) | 61 (1.5%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 19 (4.5%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 1390 (33.1%) | 0 (0%) | 14 (56%) | 0 (0%) | 58 (48.3%) | 0 (0%) | < 5 |
| Drug to treat mental health diseases (n/%) | 617 (14.7%) | 0 (0%) | 7 (28%) | 0 (0%) | 21 (17.5%) | 55 (13.1%) | < 5 |
| Lipid lowering drugs (n/%) | 561 (13.3%) | 0 (0%) | 6 (24%) | 0 (0%) | 19 (15.8%) | 41 (9.8%) | < 5 |
| Cardiovascular medication (n/%) | 1065 (25.3%) | 0 (0%) | 9 (36%) | 0 (0%) | 52 (43.3%) | 112 (26.7%) | < 5 |
| Oncologic drugs (n/%) | 55 (1.3%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | 21 (5%) | 0 (0%) |
| Anti-epileptics (n/%) | 252 (6%) | 0 (0%) | < 5 | 0 (0%) | 6 (5%) | 25 (6%) | < 5 |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (4.8%) | 0 (0%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.2.3 IRs of EN flares

#### 10.2.3.1 IRs of EN flares in the general population

The IR of the first flare episode of EN in BIFAP was 242.3 per 1,000 PY. In VID was 492.5 per 1,000 PY. In SIDIAP, the IR was 538.8 per 1,000 PY. In SNDS, was 412.3 per 1,000 PY. In NHR, the IR was 528.4 per 1,000 PY. The IRs of the second flare decreased in most of the databases. In BIFAP the incidence was 89.3 per 1,000 PY. In VID, it dropped to 59 flare cases per 1,000 PY. In SIDIAP, the IR decreased to 300.9 per 1,000 PY. In SNDS, the IR went down to 258.7 per 1,000 PY. In NHR, the rate dropped to 157.6 per 1,000 PY. The IRs of the third flare episode kept decreasing in most databases: it was 47.9 per 1,000 PY in BIFAP, 145,9 per 1,000 PY in SIDIAP, 136.8 per 1,000 PY in SNDS and none in VID. In NHR it increased at 4,198.3 per 1,000 PY.

*Table 16. Background incidence rate of first, second, and third flare in the EN cohort per 1,000 person-years (95% confidence interval).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | NA | NA | NA | NA | NA | NA | NA |
| Number of persons who started the follow-up | 4,088 | NA | 24 | 5 | 114 | 404 | 7 |
| Number of persons who develop a first flare-up episode | 1,884 | NA | 13 | 0 | 73 | 186 | 5 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 242.3 (231.5-253.5) | NA (NA-NA) | 492.5 (262.2-842.2) | 0 (0-276.1) | 538.8 (422.4-677.5) | 412.3 (355.2-476) | 528.4 (171.6-1,233.2) |
| Number of persons still in the study 90 days after first flare | 1779 | NA | 12 | NA | 71 | 176 | < 5 |
| Number of persons who develop a second flare-up episode | 283 | NA | < 5 | NA | 31 | 50 | < 5 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 89.3 (79.2-100.3) | NA (NA-NA) | 59 (1.5-328.5) | NA (NA-NA) | 300.9 (204.4-427.1) | 258.7 (192-341.1) | 157.6 (4-878.3) |
| Number of persons still in the study 90 days after second flare | 256 | NA | NA | NA | 30 | 47 | < 5 |
| Number of persons who develop a third flare-up episode | 18 | NA | NA | NA | 7 | 8 | < 5 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 47.9 (28.4-75.7) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 145.9 (58.7-300.7) | 136.8 (59.1-269.5) | 4,198.3 (106.3-23,391.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.2.3.2 IRs of EN flares stratified per age categories

Most of the people experiencing a first or second episode of EN flares were adults ≥ 18 years old and ≥ 60 years old. There were no individuals between 0-17 years old who experienced a third flare episode across all data sources. In NHR, ≤5 individuals accounted for all age categories had a first EN flare episodes.

IRs in 0-17-year-olds were higher than adults in SNDS and NHR for the first EN flare, and in SIDIAP and SNDS for the second EN flare. All of them presented high CIs as only

<5 individuals were observed in SIDIAP and NHR and 24 in SNDS. Across adults, IRs were higher or lower for 18-59 compared to ≥60 age depending on the database.
In BIFAP, the database where more EN flare-up episodes were detected, IRs of first flare episodes were almost equal for the ≥ 60-year-old population (243.6 per 1,000 PY) versus the 18-59-year-old subgroup (244,8 per 1,000 PY). Regarding the second flare episodes, IR values decreased both for the 18-59 years category (90.3 per 1,000 PY) and for the ≥60 age category (95.9 per 1,000 PY) compared to the first flare incidence. In the third EN flare episodes, IR values kept decreased. It was 39.2 per 1,000 PY in the 18-59 years category and 79.6 per 1,000 PY in the ≥60 age category.

*Table 17. Background incidence rate of first, second, and third flare in the EN cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 126 | | | 0 | < 5 | 24 | < 5 |
| Number of persons who develop a first flare-up episode | 18-59 | 1270 | | 9 | | 39 | 138 | < 5 |
| Number of persons who develop a first flare-up episode | 60+ | 488 | | < 5 | | 32 | 24 | < 5 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 215.9 (179.9-257.1) | NA (NA-NA) | NA (NA-NA) | 0 (0-276.1) | 217.1 (26.3-784.2) | 748.7 (479.7-1114) | 627.6 (15.9-3496.6) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 244.8 (231.5-258.7) | NA (NA-NA) | 382.4 (174.9-725.9) | NA (NA-NA) | 507.1 (360.6-693.2) | 399.8 (335.9-472.4) | 475.3 (57.6-1716.9) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 243.6 (222.4-266.1) | NA (NA-NA) | 1398.1 (380.9-3579.7) | NA (NA-NA) | 648.4 (443.5-915.4) | 324.6 (208-483) | 546.4 (66.2-1973.7) |
| Number of persons still in the study 90 days after first flare | 0-17 | 120 | | | | < 5 | 21 | < 5 |
| Number of persons still in the study 90 days after first flare | 18-59 | 1224 | | 9 | | 36 | 136 | < 5 |
| Number of persons still in the study 90 days after first flare | 60+ | 518 | | < 5 | | 35 | 24 | < 5 |
| Number of persons who develop a second flare-up episode | 0-17 | 11 | | | | < 5 | 5 | NR |
| Number of persons who develop a second flare-up episode | 18-59 | 196 | | 0 | | 15 | 39 | NR |
| Number of persons who develop a second flare-up episode | 60+ | 76 | | < 5 | | 15 | 6 | NR |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 53.4 (26.7-95.6) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 434.8 (11-2422.7) | 307.1 (99.7-716.6) | 0 (0-1285.7) |

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 90.3 (78.1-103.8) | NA (NA-NA) | 0 (0-322.3) | NA (NA-NA) | 281.1 (157.4-463.7) | 254.2 (180.8-347.5) | 1383.5 (35-7708.5) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 95.9 (75.6-120.1) | NA (NA-NA) | 181.3 (4.6-1009.9) | NA (NA-NA) | 316.6 (177.2-522.1) | 254.5 (93.4-554) | 0 (0-1340.7) |
| Number of persons still in the study 90 days after second flare | 0-17 | 9 | | | | < 5 | 5 | NR |
| Number of persons still in the study 90 days after second flare | 18-59 | 182 | | | | 13 | 36 | NR |
| Number of persons still in the study 90 days after second flare | 60+ | 71 | | | | 17 | 6 | NR |
| Number of persons who develop a third flare-up episode | 0-17 | 0 | | | | 0 | 0 | NR |
| Number of persons who develop a third flare-up episode | 18-59 | 11 | | | | < 5 | 7 | NR |
| Number of persons who develop a third flare-up episode | 60+ | 7 | | | | 5 | < 5 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 0 (0-535.9) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 0 (0-1134.1) | 0 (0-436.7) | NA (NA-NA) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 39.2 (19.6-70.1) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 68.2 (8.3-246.3) | 152.3 (61.2-313.7) | 4,198.3 (106.3-2,3391.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 79.6 (32-163.9) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 325.1 (105.5-758.6) | 245.8 (6.2-1369.5) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.2.3.3 IRs of EN flares stratified per gender

Across all data sources, the number of females experiencing a first, second, or third episode of EN flares was higher than of males, as shown in Table 18.

This is in line with the reported evidence about EN being a disease that mainly affects females (37,38). Considering IRs, values are usually also higher in females than males across data sources and number of episodes.

Regarding the incidence of EN flare first episode cases, IRs were observed to be higher for females rather than males in VID (females: 602.3 per 1,000 PY; males: 246 per 1,000 PY), SNDS (females: 456.3 per 1,000 PY; males: 318.8 per 1,000 PY) and NHR (females: 736.7 per 1,000 PY; males: 0 per 1,000 PY), while comparable in BIFAP (females: 249.9 per 1,000 PY; males: 212 per 1,000 PY) and SIDIAP (females: 534.7 per 1,000 PY; males: 555.3 per 1,000 PY).

Regarding the second flare episodes, IRs were observed to be also higher for females rather than males in VID (females: 65.8 per 1,000 PY; males: 0 per 1,000 PY), SNDS (females: 273.4 per 1,000 PY; males: 221 per 1,000 PY) and NHR (females: 157.6 per 1,000 PY; males: 0 per 1,000 PY), while IRs were again comparable across males and females for BIFAP (females: 89.5 per 1,000 PY; males: 88.4 per 1,000 PY). In SIDIAP,

IRs were lower for females compared with males (females: 292.5 per 1,000 PY; males: 333.5 per 1,000 PY).
When it comes to the third flare episodes, IRs were higher for females rather than males in VID (females: 52.5 per 1,000 PY; males: 19.3 per 1,000 PY), SIDIAP (females: 152.2 per 1,000 PY; males: 132.3 per 1,000 PY) and NHR (females: 4,198.3 per 1,000 PY; males: 0 per 1,000 PY), while IRs were again comparable across males and females for BIFAP (females: 89.5 per 1,000 PY; males: 88.4 per 1,000 PY). In SIDIAP, IRs were lower for females compared with males (females: 292.5 per 1,000 PY; males: 333.5 per 1,000 PY). No people experienced a third flare episode in VID.

*Table 18. Background incidence rate of first, second, and third flare in the EN cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 1553 | | 11 | 0 | 58 | 140 | 5 |
| Number of persons who develop a first flare-up episode | M | 331 | | < 5 | 0 | 15 | 46 | 0 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 249.9 (237.6-262.6) | NA (NA-NA) | 602.3 (300.7-1077.6) | 0 (0-415.7) | 534.7 (406.1-691.3) | 456.3 (383.8-538.4) | 736.7 (239.2-1719.2) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 212.3 (190.1-236.5) | NA (NA-NA) | 246 (29.8-888.5) | 0 (0-822.1) | 555.3 (310.8-915.9) | 318.8 (233.4-425.2) | 0 (0-1379.1) |
| Number of persons still in the study 90 days after first flare | F | 1480 | | 10 | | 56 | 130 | NR |
| Number of persons still in the study 90 days after first flare | M | 299 | | < 5 | | 15 | 46 | NR |
| Number of persons who develop a second flare-up episode | F | 237 | | < 5 | | 24 | 38 | NR |
| Number of persons who develop a second flare-up episode | M | 46 | | 0 | | 7 | 12 | NR |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 89.5 (78.4-101.6) | NA (NA-NA) | 65.8 (1.7-366.4) | NA (NA-NA) | 292.5 (187.4-435.2) | 273.4 (193.5-375.3) | 157.6 (4-878.3) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 88.4 (64.7-118) | NA (NA-NA) | 0 (0-2102) | NA (NA-NA) | 333.5 (134.1-687.1) | 221 (114.2-386.1) | NA (NA-NA) |
| Number of persons still in the study 90 days after second flare | F | 217 | | | | 23 | 37 | NR |
| Number of persons still in the study 90 days after second flare | M | 39 | | | | 7 | 10 | NR |
| Number of persons who develop a third flare-up episode | F | 17 | | | | 5 | 6 | NR |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | M | < 5 | | | | < 5 | < 5 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 52.5 (30.6-84.1) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 152.2 (49.4-355.2) | 133.5 (49-290.6) | 4,198.3 (106.3-23391.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 19.3 (0.5-107.6) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 132.3 (16-478) | 147.6 (17.9-533.3) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.2.3.4 IRs of EN flares in pregnant population

BIFAP, CPRD, PEDIANET (adolescents up to 14 years of age), SNDS did not run the pregnancy algorithm. VID and SIDAP identified pregnant population in the EN incident cohort, in both cases, less than 5 persons. No cases were reported of individuals developing a first or second flare-up episodes while pregnant across all databases. See Table 19 below.

*Table 19. Background IR in pregnant population of first, second, and third flare in the EN cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | < 5 | NA | < 5 | NA | NA |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 0 | NA | 0 | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA (NA-NA) | NA (NA-NA) | 0 (0-3,536.4) | NA (NA-NA) | 0 (0-4,794.9) | NA (NA-NA) | NA (NA-NA) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | < 5 | NA | < 5 | NA | NA |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | 0 | NA | 0 | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA (NA-NA) | NA (NA-NA) | 0 (0-4,794.9) | NA (NA-NA) | 0 (0-10,207.3) | NA (NA-NA) | NA (NA-NA) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | NA | NA | NA | NA | NA |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | < 5 | NA | < 5 | NA | NA |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 | NA | 0 | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.2.4 Six- and twelve-months cumulative incidence of flares of EN

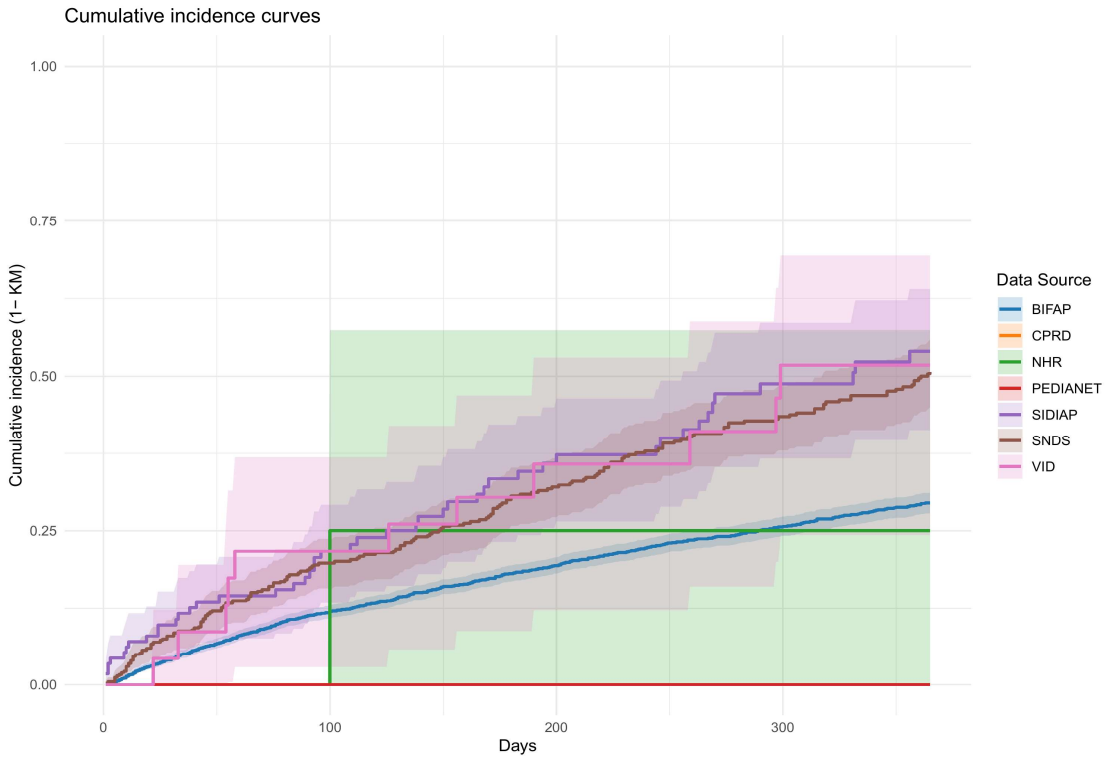
Table 20 shows the 6- and 12-months cumulative incidence of a first flare episode of EN. The 6-month risk of a first flare in an EN patient was 18.1% in BIFAP, 30.4% in VID, 33.4% in SIDIAP, 30.6% in SNDS and 25% in NHR. The risk of EN patients having a first flare of EN during the 1-year timespan was 29.5% in BIFAP, 51.8% in VID, 54% in SIDIAP, 50.7% in SNDS and 25% in NHR. The cumulative incidence curve is plotted in Figure 6.

*Table 20. Six- and twelve-months cumulative incidence of flares of EN (95% confidence interval).*

| Days | BIFAP-ES | VID-ES | SIDIAP-ES | PEDIANET-IT | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| 180 | 0.181 (0.168-0.194) | 0.304 (0.088-0.469) | 0.334 (0.232-0.422) | 0 (0-0) | 0.306 (0.258-0.352) | 0.25 (0-0.574) |
| 365 | 0.295 (0.278-0.311) | 0.518 (0.243-0.694) | 0.54 (0.413-0.64) | 0 (0-0) | 0.507 (0.45-0.559) | 0.25 (0-0.574) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 6. Cumulative incidence curve EN*

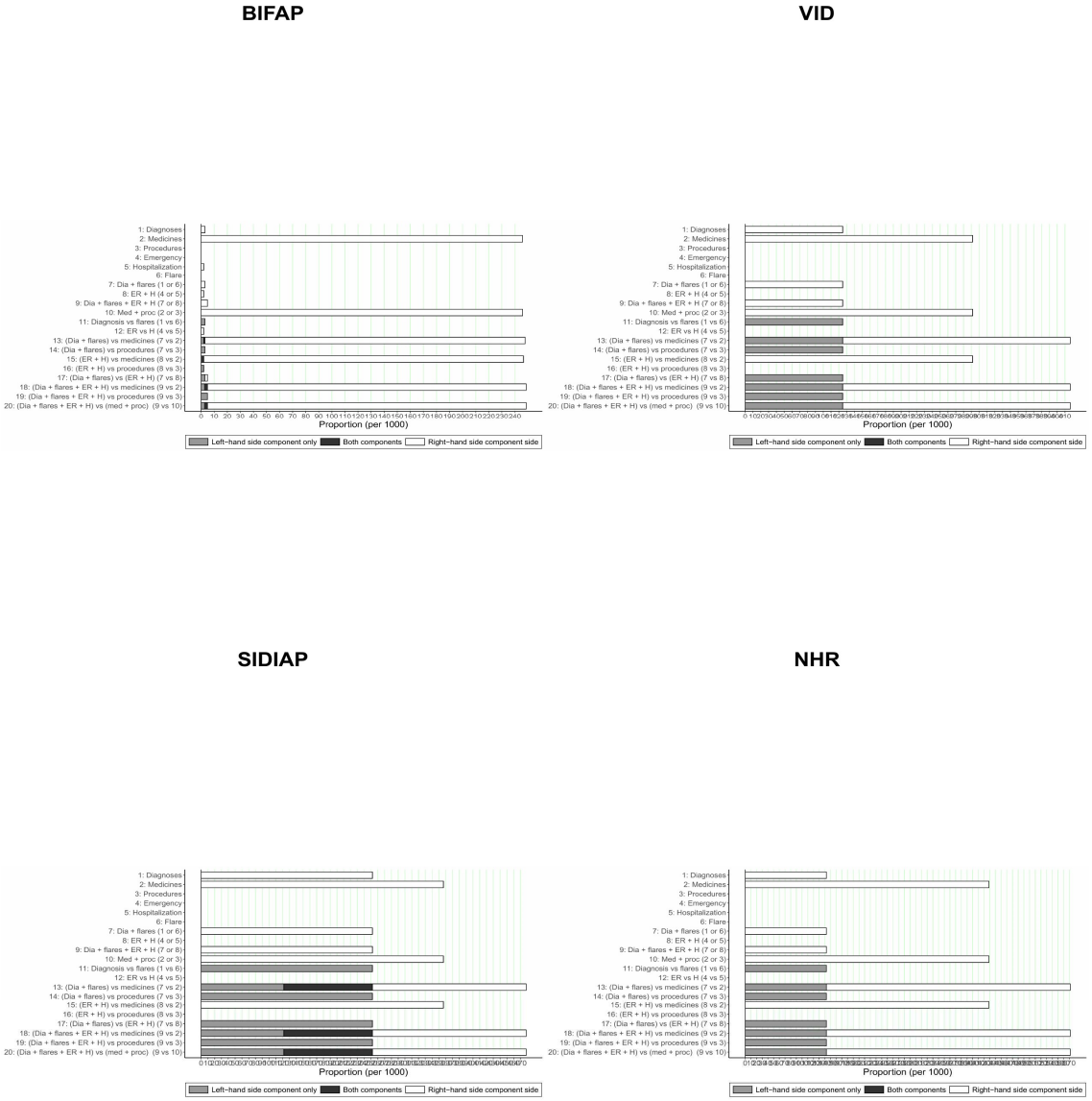



### 10.2.5 Other analyses

#### 10.2.5.1 Component analysis

Considering the components used to identify EN flares (see Figure 7), MED accounted for the highest 12-month cumulative incidence of the first episode across VID, SIDIAP, BIFAP and NHR, ranging from 66.7% in NHR to 76.9% in VID. The remaining cases were identified through DIA. The overlapping identification of cases through MED and DIA ranged from 0% (NHR) to 26.3% (SIDIAP).

*Figure 7. Component Analyses for EN.*



## 10.3 GRAVES DISEASE (GD)

### 10.3.1 Attrition of study population

The number of study subjects with GD who started the follow up 90 days after diagnosis were 48,855 in BIFAP, 45,943 in CPRD, 27,645 in VID, 5 in PEDIANET, 37,879 in SIDIAP, 9,830 in SNDS, and 15,919 in NHR, all accounting for more than 86.7% of the total cohort population with GD. See Table 21 below.

*Table 21. Attrition table for the Graves' Disease cohort.*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking requiring data | 10,359,326* | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 56,151 | 62,386 | 33,586 | 6 | 43,545 | 12,460 | 21,921 |
| Disease codes found during lookback | 7,294 | 14,071 | 3,418 | < 5 | 3,161 | 1,126 | 5,128 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Graves' disease | 48,857 | 48,315 | 30,168 | 5 | 40,384 | 11,334 | 16,793 |
| Persons dying before entrance in the follow-up | 1,231 | 376 | 461 | 0 | 764 | 776 | 71 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 2,141 | 1,996 | 2,062 | 0 | 1,741 | 728 | 803 |
| Persons entering follow-up | 45,485 | 45,943 | 27,645 | 5 | 37,879 | 9,830 | 15,919 |

*BIFAP-ES contributed to this study with a subset of linked PC-hospital data only. It leaves 48.4% of the data instance population (PC only) out of the study population.
NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.3.2 Characteristics of the study cohort

The age range of GD patients at first diagnosis was 49 (NHR) to 68 years old (SNDS), except in PEDIANET where it was 6 years of age. Between 71% to 78.4% of the GD patients were females. The male-to-female sex ratio in GD incident cases across databases

was 35 males to every 100 females. Both median age and sex distribution are compatible with demographic knowledge of GD in the general population (39). The total follow-up time ranged from 17,428 PY in SNDS to 142,355 in CPRD. PEDIANET is an exception with 9 PY. See Table 22 below.

*Table 22. Characteristics of the GD cohort population.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 48,857 | 48,315 | 30,168 | 5 | 40,384 | 11,334 | 16,793 |
| Female (n/%) | 35,008 (71.7%) | 37,403 (77.4%) | 22,976 (76.2%) | < 5 | 28,977 (71.8%) | 8,044 (71%) | 13,166 (78.4%) |
| Male (n/%) | 13,849 (28.3%) | 10,910 (22.6%) | 7,192 (23.8%) | < 5 | 11,407 (28.2%) | 3,290 (29%) | 3,627 (21.6%) |
| Other (n/%) | 0 (0%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 41 | 38 | 44 | 4 | 42 | 51 | 35 |
| Age in year (IQR): PCT 50 | 57 | 52 | 57 | 6 | 56 | 68 | 49 |
| Age in year (IQR): PCT 75 | 75 | 67 | 72 | 8 | 73 | 82 | 63 |
| Age in categories (n/%): < 18 | 1,208 (2.5%) | 1,145 (2.4%) | 409 (1.4%) | 5 (100%) | 803 (2%) | 70 (0.6%) | 486 (2.9%) |
| Age in categories (n/%): 18-59 | 25,247 (51.7%) | 29,508 (61.1%) | 16,213 (53.7%) | 0 (0%) | 21,392 (53%) | 4,107 (36.2%) | 11,368 (67.7%) |
| Age in categories (n/%): > 60 | 22,402 (45.9%) | 17,662 (36.6%) | 13,546 (44.9%) | 0 (0%) | 18,189 (45%) | 7,157 (63.1%) | 4,939 (29.4%) |
| Number of persons who started the follow-up | 45,485 (93.1%) | 45,943 (95.1%) | 27,645 (91.6%) | 5 (100%) | 37,879 (93.8%) | 9,830 (86.7%) | 15,919 (94.8%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 137,499 | 142,355 | 34,961 | 9 | 113,642 | 17,428 | 43,552 |
| Number of vaccinations during follow-up (median, IQR) | 2 | 0 | 0 | 2 | 2 | 0 | 3 |
| Number of people with vaccinations (n/%): 0 | 12,475 (25.5%) | 38,913 (80.5%) | 17,075 (56.6%) | < 5 | 11,627 (28.8%) | 5,316 (46.9%) | 2,984 (17.8%) |
| Number of people with vaccinations (n/%): 1 | 5,094 (10.4%) | 3,342 (6.9%) | 5,946 (19.7%) | 0 (0%) | 3,291 (8.1%) | 1,775 (15.7%) | 1,515 (9%) |
| Number of people with vaccinations (n/%): 2 | 6,665 (13.6%) | 1,572 (3.3%) | 3,889 (12.9%) | < 5 | 6,137 (15.2%) | 1,300 (11.5%) | 2,101 (12.5%) |
| Number of people with vaccinations (n/%): 3 or more | 21,251 (43.5%) | 2,116 (4.4%) | 735 (2.4%) | < 5 | 16,824 (41.7%) | 1,439 (12.7%) | 9,319 (55.5%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 23 describes comorbidities at baseline of GD patients. From 3% (CPRD) to up to 10.6% (NHR) of the GD population had a code or drug implying an immunocompromised status during the look-back period. Cancer diagnosis in the look back period ranged from 3.8% (CPRD) to 10.2% (SNDS), except for PEDIANET (0%). Occurrence of at least one infection during the look-back period was 59.1% in SNDS, 36.7% in CPRD, 36,1% in BIFAP, 40.4% in VID, 36.2% in SIDIAP and 33.4% in NHR.

SNDS reports the highest prevalence of drug use across most therapeutic groups. Of note, the use of systemic corticosteroids in SNDS (29%) almost triples the reported use in BIFAP (9.2%), CPRD (8.8%), VID (9.5%), SIDIAP (9.8%) and NHR (10,4%). Prevalence of antibiotic use in GD patients during look back was between 29.1 and 55.4% across databases, except in PEDIANET (<5 counts).

*Table 23. Comorbidities in the study cohort with Graves' disease.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 48,857 | 48,315 | 30,168 | 5 | 40,384 | 11,334 | 16,793 |
| Immunocompromise status (n/%) | 1,625 (3.3%) | 1,464 (3%) | 2,195 (7.3%) | 0 (0%) | 1,641 (4.1%) | 708 (6.2%) | 1,772 (10.6%) |
| Malignancy (n/%) | 2,002 (4.1%) | 1,842 (3.8%) | 1,599 (5.3%) | 0 (0%) | 1,565 (3.9%) | 1,154 (10.2%) | 1,158 (6.9%) |
| Infection (n/%) | 17,624 (36.1%) | 17,755 (36.7%) | 12,192 (40.4%) | < 5 | 14,606 (36.2%) | 66,95 (59.1%) | 5,613 (33.4%) |
| Hepatitis C (n/%) | 85 (0.2%) | 5 (0%) | 57 (0.2%) | 0 (0%) | 71 (0.2%) | 9 (0.1%) | 13 (0.1%) |
| Immunostimulants (n/%) | < 5 | 5 (0%) | 56 (0.2%) | 0 (0%) | 0 (0%) | 131 (1.2%) | 52 (0.3%) |
| Analgesics (n/%) | 21,312 (43.6%) | 12,532 (25.9%) | 16,061 (53.2%) | 0 (0%) | 19,061 (47.2%) | 8,918 (78.7%) | 4,685 (27.9%) |
| Systemic corticosteroids (n/%) | 4,478 (9.2%) | 4,264 (8.8%) | 2,878 (9.5%) | < 5 | 3,969 (9.8%) | 3,291 (29%) | 1,746 (10.4%) |
| Antithrombotic agents (n/%) | 10,959 (22.4%) | 7,915 (16.4%) | 6,378 (21.1%) | 0 (0%) | 8,803 (21.8%) | 4,871 (43%) | 3,189 (19%) |
| Sex hormones (n/%) | 1,925 (3.9%) | 6,977 (14.4%) | 1,336 (4.4%) | 0 (0%) | 1,515 (3.8%) | 1,167 (10.3%) | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 4,706 (9.6%) | 4,619 (9.6%) | 3,103 (10.3%) | < 5 | 4,142 (10.3%) | 3,362 (29.7%) | 1,922 (11.4%) |
| Diabetes medications (n/%) | 5,776 (11.8%) | 4,575 (9.5%) | 3,940 (13.1%) | 0 (0%) | 4,998 (12.4%) | 2,021 (17.8%) | 1,220 (7.3%) |
| Antibiotics (n/%) | 14496 (29.7%) | 16953 (35.1%) | 11481 (38.1%) | < 5 | 13015 (32.2%) | 6275 (55.4%) | 4880 (29.1%) |
| Antiviral drugs (n/%) | 535 (1.1%) | 626 (1.3%) | 467 (1.5%) | 0 (0%) | 420 (1%) | 419 (3.7%) | 389 (2.3%) |
| Antimycotics (n/%) | 493 (1%) | 770 (1.6%) | 0 (0%) | 0 (0%) | 431 (1.1%) | 585 (5.2%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 12,345 (25.3%) | 5,165 (10.7%) | 11,510 (38.2%) | 0 (0%) | 11,510 (28.5%) | 0 (0%) | 4,173 (24.8%) |
| Drug to treat mental health diseases (n/%) | 9,540 (19.5%) | 12,047 (24.9%) | 6,722 (22.3%) | 0 (0%) | 8,748 (21.7%) | 2,756 (24.3%) | 2,425 (14.4%) |
| Lipid lowering drugs (n/%) | 10,418 (21.3%) | 10,012 (20.7%) | 8,191 (27.2%) | 0 (0%) | 8,546 (21.2%) | 3,153 (27.8%) | 2,702 (16.1%) |
| Cardiovascular medication (n/%) | 21,009 (43%) | 19,708 (40.8%) | 15,160 (50.3%) | 0 (0%) | 18,983 (47%) | 7,854 (69.3%) | 2,781 (16.6%) |
| Oncologic drugs (n/%) | 709 (1.5%) | 1,022 (2.1%) | 615 (2%) | 0 (0%) | 511 (1.3%) | 519 (4.6%) | 240 (1.4%) |
| Anti-epileptics (n/%) | 3,553 (7.3%) | 933 (1.9%) | 2,621 (8.7%) | 0 (0%) | 3,310 (8.2%) | 1,105 (9.7%) | 729 (4.3%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 21 (0%) | 83 (0.3%) | 0 (0%) | 0 (0%) | 36 (0.3%) | 79 (0.5%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.3.3 IRs of GD flares

#### 10.3.3.1 IRs of GD flares in the general population

There was a great variability in IRs of the first flare episode of GD across databases. In CPRD, the IR per 1,000 PY was low: 0.1. It increased from 11.8 in VID and 25,1 per 1,000 PY in NHR, to 101.2 per 1,000 PY in SIDIAP, 104.9 in SNDS, and 118.5 in BIFAP.

Finally, it was 227.4 in PEDIANET but with wide confidence intervals due to low number of people observed having the episode (<5).
The IRs of the second flares increased in all databases, from 71 in per 1,000 PY in VID to 438 per 1,000 PY in SIDIAP. PEDIANET reported a very high IR of the second flare also with a wide confidence interval again with <5 people experiencing the second flare episode. The IR of the third flare raised in relation to the second flare in BIFAP (472.4 per 1,000 PY), in SIDIAP (567.4 per 1,000 PY), in SNDS (713.4 per 1,000 PY), and in NHR (157.5 per 1,000 PY). The IR in PEDIANET was very high (8494.2 per 1,000 PY with wide confidence interval) with 5 cohort participants. There were no third flare cases in CPRD and VID.

*Table 24. Background incidence rate of first, second, and third flare in the GD cohort per 1,000 person-years (95% confidence interval).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 48,857 | 48,315 | 30,168 | 5 | 40,384 | 11,334 | 16,793 |
| Number of persons who started the follow-up | 45,476 | 45,943 | 27,642 | 5 | 37,876 | 9,807 | 15,908 |
| Number of persons who develop a first flare-up episode | 10,651 | 12 | 367 | < 5 | 7,846 | 1,428 | 805 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 118.5 (116.2-120.7) | 0.1 (0-0.2) | 11.8 (10.7-13.1) | 227.4 (5.8-1267.1) | 101.2 (98.9-103.4) | 104.9 (99.5-110.4) | 25.1 (23.4-26.9) |
| Number of persons still in the study 90 days after first flare | 9,888 | 12 | 311 | < 5 | 7,592 | 1,251 | 741 |
| Number of persons who develop a second flare-up episode | 4,435 | < 5 | 15 | < 5 | 3,629 | 426 | 116 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 355.6 (345.2-366.2) | 102.3 (12.4-369.4) | 71 (39.7-117.1) | 3069.3 (77.7-17101.2) | 438 (423.9-452.5) | 392.1 (355.8-431.2) | 105.9 (87.5-127.1) |
| Number of persons still in the study 90 days after second flare | 4,049 | < 5 | 9 | < 5 | 3,483 | 350 | 105 |
| Number of persons who develop a third flare-up episode | 1,925 | 0 | 0 | < 5 | 1,760 | 145 | 20 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 472.4 (451.6-494) | 0 (0-1570.4) | 0 (0-854.4) | 8494.2 (215.1-47326.6) | 567.4 (541.2-594.5) | 713.4 (602-839.5) | 157.5 (96.2-243.2) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.3.3.2 IRs of GD flares stratified per age categories

Most of the people experiencing flares of GD were adults ≥ 18 years old and ≥60 years old. Overall, the incidence of flares increased from the first episode to the third one for all the data sources, especially detectable in BIFAP, SIDIAP, SNDS and NHR where people experiencing a second and third flare were observed. No cases for adults in PEDIANET as those age categories are not in this database.
IRs in 0-17-year-olds were higher than all adult categories in all data sources and across flare episodes, while variability across data sources and episodes without a clear pattern was observed for 18-59 and ≥60 age individuals' IRs.

Across data sources, for the 0-17-year-old category, the IRs of the first flare ranged from 12.8 (VID) to 390 (SNDS) per 1000 PY, the IRs of the second flare episodes span from 497.3 (NHR) to 527. 6 (BIFAP) per 1000 PY with no or <5 cases in VID and PEDIANET, respectively, and the IRs of the third flare episodes were 676.1 in BIFAP and 644.9 in SIDIAP per 1000 PY with no or <5 cases for the other data sources. For the 18–59-year-old category, the IRs per 1000 PY of the first flare ranged from 14.4 (VID) to 126.8 (BIFAP), the rates of the second flare episodes were from 86.1 (NHR) to 412.5 (SNDS), and the IRs of the third episode span from 124 (NHR) to 595.2 (SNDS) with no cases for VID. For the ≥60-year-old category, the IRs per 1000 PY ranged from 8.4 (VID) to 110.8 (SNDS) for the first flare, while IRs were from 148.4 (NHR) to 537.9 (SIDIAP) for the second flare episodes and span from 154.8 (NHR, <5 cases) to 838 (SNDS) for the third flare episodes. No, or <5 cases were observed for CPRD for this age category across all episodes.

*Table 25. Background incidence rate of first, second, and third flare in the GD cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 224 | 0 | < 5 | < 5 | 154 | 21 | 19 |
| Number of persons who develop a first flare-up episode | 18-59 | 6,380 | 9 | 252 | NA | 4,381 | 553 | 572 |
| Number of persons who develop a first flare-up episode | 60+ | 4047 | < 5 | 111 | NA | 3,311 | 854 | 214 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 124.7 (108.9-142.1) | 0 (0-1.8) | 12.8 (3.5-32.8) | 227.4 (5.8-1267.1) | 143.4 (121.7-168) | 390 (241.4-596.2) | 27.4 (16.5-42.8) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 126.8 (123.7-129.9) | 0.1 (0-0.2) | 14.4 (12.7-16.3) | NA | 100.4 (97.4-103.4) | 94.5 (86.8-102.7) | 25.7 (23.6-27.9) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 107.1 (103.8-110.4) | 0.1 (0-0.2) | 8.4 (6.9-10.2) | NA | 100.8 (97.4-104.3) | 110.8 (103.5-118.4) | 23.5 (20.4-26.8) |
| Number of persons still in the study 90 days after first flare | 0-17 | 195 | | < 5 | < 5 | 144 | 18 | 16 |
| Number of persons still in the study 90 days after first flare | 18-59 | 6,023 | 9 | 213 | NA | 4,357 | 497 | 530 |
| Number of persons still in the study 90 days after first flare | 60+ | 3,969 | < 5 | 99 | NA | 3,292 | 760 | 226 |
| Number of persons who develop a second flare-up episode | 0-17 | 87 | | 0 | < 5 | 66 | 7 | 6 |
| Number of persons who develop a second flare-up episode | 18-59 | 2,714 | < 5 | 13 | NA | 1,934 | 176 | 70 |
| Number of persons who develop a second flare-up episode | 60+ | 1,634 | 0 | < 5 | NA | 1,629 | 243 | 40 |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 527.6 (422.6-650.8) | NA | 0 (0-3027.8) | 3069.3 (77.7-17101.2) | 721 (557.6-917.3) | 511.2 (205.5-1053.4) | 497.3 (182.5-1082.4) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 341.2 (328.5-354.3) | 137.4 (16.6-496.3) | 89.7 (47.8-153.4) | NA | 374.5 (358-391.5) | 412.5 (353.8-478.2) | 86.1 (67.1-108.7) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 375.5 (357.5-394.1) | 0 (0-737.5) | 30.7 (3.7-110.8) | NA | 537.9 (512.1-564.7) | 376.1 (330.3-426.5) | 148.4 (106-202) |
| Number of persons still in the study 90 days after second flare | 0-17 | 76 | | | < 5 | 65 | < 5 | 6 |
| Number of persons still in the study 90 days after second flare | 18-59 | 2,509 | < 5 | 7 | NA | 1,911 | 157 | 64 |
| Number of persons still in the study 90 days after second flare | 60+ | 1,566 | | < 5 | NA | 1,588 | 189 | 43 |
| Number of persons who develop a third flare-up episode | 0-17 | 34 | | | < 5 | 30 | < 5 | NR |
| Number of persons who develop a third flare-up episode | 18-59 | 1,186 | 0 | 0 | NA | 836 | 65 | NR |
| Number of persons who develop a third flare-up episode | 60+ | 705 | | 0 | NA | 894 | 78 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 676.1 (468.2-944.8) | NA | NA | 8494.2 (215.1-47326.6) | 644.9 (435.1-920.7) | 2,117.4 (256.4-7,648.7) | 2,692.3 (555.2-7,867.9) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 455.9 (430.4-482.7) | 0 (0-1570.4) | 0 (0-982) | NA | 433.8 (404.9-464.2) | 595.2 (459.3-758.6) | 124 (59.4-228) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 495.4 (459.5-533.4) | NA | 0 (0-6572.5) | NA | 792.4 (741.3-846.1) | 838 (662.4-1,045.8) | 154.8 (62.2-318.9) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.3.3.3 IRs of GD flares stratified per gender

Across all data sources, the number of females experiencing a first, second, or third episode of GD flares was higher than that of males, as shown in Table 26.
This is in line with the reported evidence about GD being a disease that mainly affects females (40). Overall, first flares' IRs were higher for females while higher for males for second episodes except SNDS and no clear pattern was observed for third episodes.
Regarding the first episodes, IRs were observed to be higher for females rather than males across data sources, with values per 1000 PY for females ranging from 0.1 (CPRD) to 124.2 (BIFAP), while PEDIANET shows <5 females experiencing the event (984.5 per 1000 PY). On the other hand, male IRs per 1000 PY were from 22.4 (NHR) to 104.3 (SNDS), with no cases in PEDIANET and <5 in CPRD (IR = 0.1 per 1000 PY).
IRs per 1000 PY of second episodes were observed to be higher for females rather than males only for SNDS (females: 417.9; males: 313.3), while higher IRs for males were

found in BIFAP (females: 350.3; males: 373.7), SIDIAP (females: 431.2; males: 460.4), and NHR (females: 99.5; males: 132.9). Similar values between gender categories were present in VID (females: 70.8; males: 71.6 but <5 observed cases). CPRD reported <5 cases for females (IR = 155.9 per 1000 PY) while no cases for males. PEDIANET has <5 cases in males (IR = 3,069.3 per 1000 PY) and no cases in females.
More than 5 cases of a third flare episode were reported only in BIFAP, SIDIAP and SNDS. IRs per 1000 PY were higher for males in SIDIAP (females: 546.6; males: 637.7) and SNDS (females: 680.4; males: 894.8) while almost comparable between genders in BIFAP (females: 474.6; males: 465.4). NHR showed <5 cases in both females (IR = 177 per 1000 PY) and males (IR = 96.8 per 1000 PY), while PEDIANET has <5 cases in females (IR = 8,494.2 per 1000 PY). No cases were reported for all the other data sources and gender populations.

*Table 26 Background incidence rate of first, second, and third flare in the GD cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 8,097 | 9 | 290 | < 5 | 5,931 | 1,053 | 652 |
| Number of persons who develop a first flare-up episode | M | 2,554 | < 5 | 77 | 0 | 1,915 | 375 | 153 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 124.2 (121.5-126.9) | 0.1 (0-0.2) | 12 (10.7-13.5) | 984.5 (24.9-5485.3) | 105.3 (102.6-108) | 105.1 (98.8-111.6) | 25.8 (23.9-27.9) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 103.4 (99.4-107.5) | 0.1 (0-0.3) | 11.3 (8.9-14.1) | 0 (0-1091) | 90.3 (86.3-94.4) | 104.3 (94-115.4) | 22.4 (19-26.3) |
| Number of persons still in the study 90 days after first flare | F | 7,540 | 9 | 242 | < 5 | 5,740 | 933 | 593 |
| Number of persons still in the study 90 days after first flare | M | 2,348 | < 5 | 69 |  | 1,852 | 318 | 148 |
| Number of persons who develop a second flare-up episode | F | 3,382 | < 5 | 12 | < 5 | 2,740 | 342 | 88 |
| Number of persons who develop a second flare-up episode | M | 1,053 | 0 | < 5 |  | 889 | 84 | 28 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 350.3 (338.6-362.3) | 155.9 (18.9-563) | 70.8 (36.6-123.7) | 3,069.3 (77.7-17101.2) | 431.2 (415.2-447.7) | 417.9 (374.8-464.7) | 99.5 (79.8-122.6) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 373.7 (351.5-397) | 0 (0-548.4) | 71.6 (14.8-209.3) | NA | 460.4 (430.6-491.7) | 313.3 (249.9-387.9) | 132.9 (88.3-192.1) |
| Number of persons still in the study 90 days after second flare | F | 3,092 | < 5 | 8 | < 5 | 2,635 | 285 | 81 |
| Number of persons still in the study 90 days after second flare | M | 957 |  | < 5 |  | 848 | 65 | 24 |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | F | 1,477 | 0 | 0 | < 5 | 1,310 | 117 | NR |
| Number of persons who develop a third flare-up episode | M | 448 | | 0 | | 450 | 28 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 474.6 (450.7-499.4) | 0 (0-1570.4) | 0 (0-859.8) | 8,494.2 (215.1-47,326.6) | 546.6 (517.4-577.1) | 680.4 (562.8-815.5) | 177 (103.1-283.5) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 465.4 (423.3-510.6) | NA | 0 (0-134,736.3) | NA | 637.7 (580.2-699.5) | 894.8 (594.6-1,293.2) | 96.8 (20-282.8) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.3.3.4 IRs of GD flares in pregnant population

Pregnant persons in the cohort of GD patients were identified in VID, SIDIAP, and NHR. BIFAP, CPRD, SNDS and PEDIANET did not deploy the ConcePTION pregnancy algorithm, therefore did not identified pregnancies along the study period. The IRs of the first flare episode in pregnant people with GD was 11.5 per 1000 PY in VID and 13.1 per 1000 PY in NHR. The IR of the first flare increased to 101.5 per 1000 PY in SIDIAP. The IRs of the second flare increased importantly but such values are affected by small numbers of people experiencing the event. This also happened in the estimates of the third flare.

*Table 27. Background IR in pregnant population with GD of first, second, and third flare per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 646 | 490 | NA | 1,093 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | < 5 | 24 | NA | 7 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 11.5 (2.4-33.5) | 101.5 (65-151) | NA | 13.1 (5.3-26.9) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | 7 | 68 | NA | 50 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | 0 | 13 | NA | < 5 |
| IR of second flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-1653.2) | 471 (250.8-805.4) | NA | 37.7 (1-210.3) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | NA | 21 | NA | < 5 |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | NA | < 5 | NA | 0 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | 565.4 (154.1-1447.7) | NA | 0 (0-3126.1) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.3.4 Six- and twelve-months cumulative incidence of GD flares

Table 28 shows the 6- and 12-months cumulative incidence of the first flare episode of GD. The 6-month risk of a first flare was 2.5% in NHR, 0.8% in VID, 10.9% in SIDIAP,

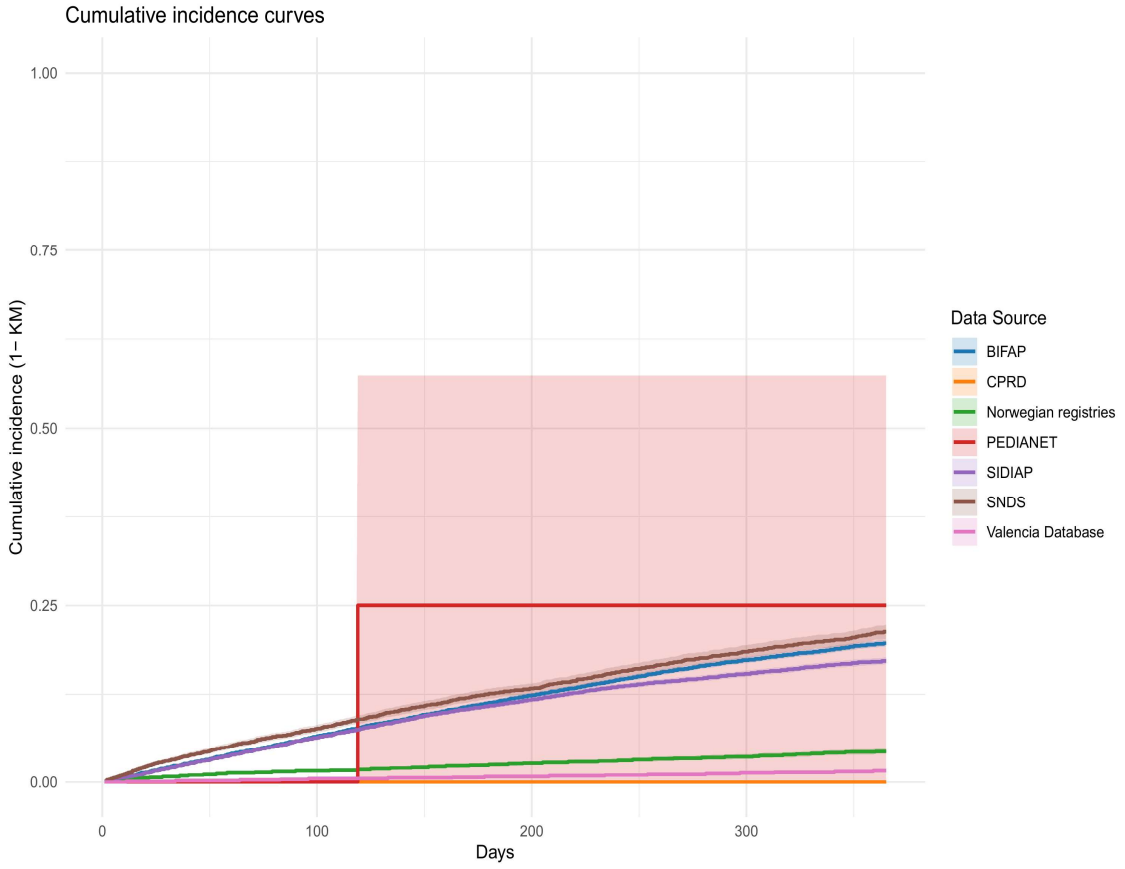
11.3 in BIFAP, 25% in PEDIANET and 12.6% in SNDS. The risk of at least one flare episode during a 1-year timespan was 4.4% in NHR, 1.6% in VID, 17.2% in SIDIAP, 19.7 in BIFAP, 25% in PEDIANET, and 21.3% in SNDS. A cumulative incidence curve is plotted in Figure 8**.**

*Table 28. Six- and twelve-months cumulative incidence of GD flares (95% confidence interval).*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | PEDIANET-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|---|
| 180 | 0.025 (0.022-0.027) | 0.008 (0.006-0.009) | 0.109 (0.105-0.112) | 0.113 (0.109-0.116) | 0.25 (0-0.574) | 0.126 (0.119-0.133) | 0 (0-0) |
| 365 | 0.044 (0.04-0.048) | 0.016 (0.014-0.018) | 0.172 (0.168-0.177) | 0.197 (0.193-0.202) | 0.25 (0-0.574) | 0.213 (0.203-0.223) | 0 (0-0) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 8. Cumulative incidence curve after a first flare episode of GD.*




### 10.3.5 Other analyses

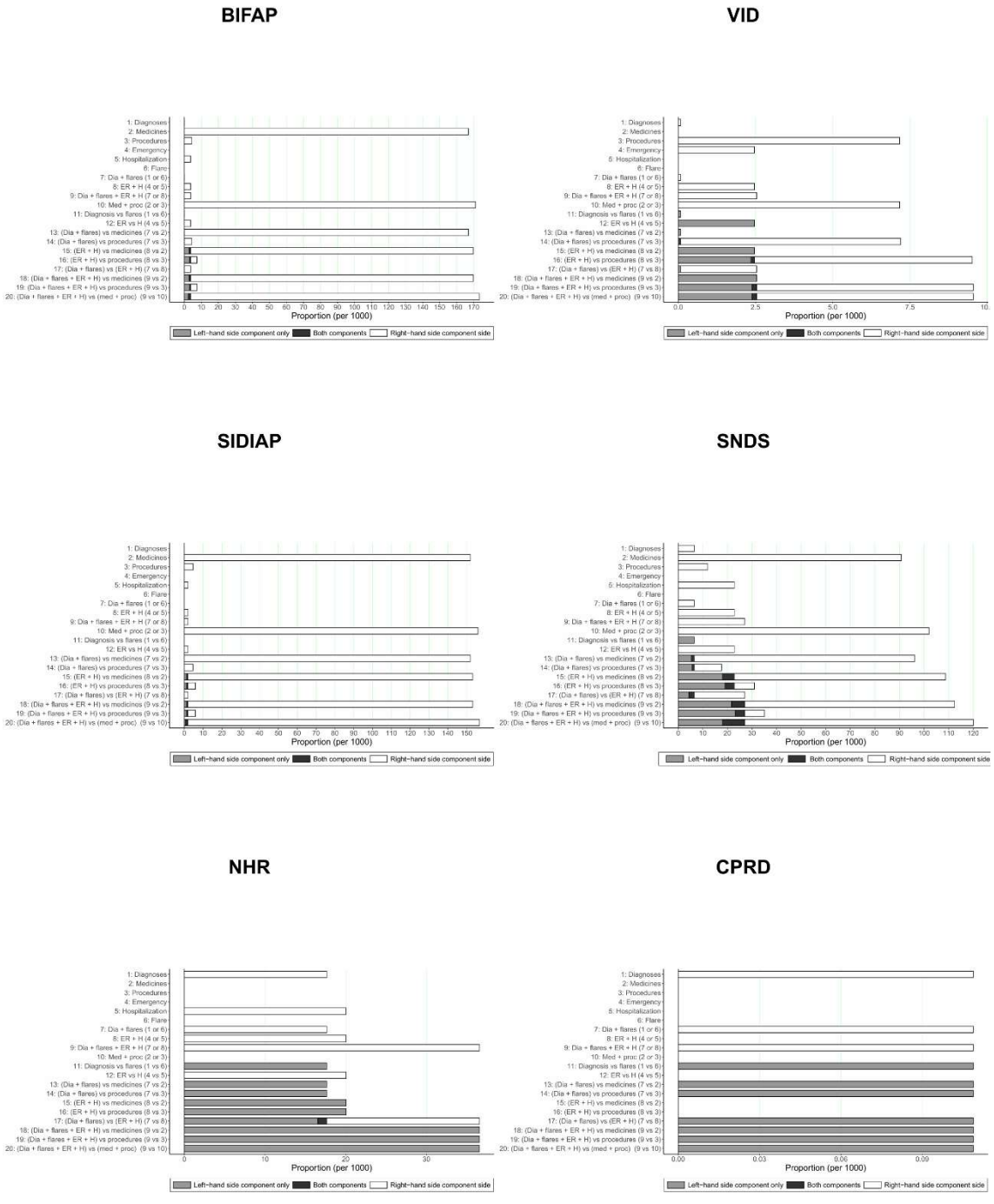
#### 10.3.5.1 Component analysis

Considering the components used to identify GD flares (see

Figure 9), variability was observed across data sources. MED accounted for the highest 12-month cumulative incidence of the first episode in SNDS (75%), BIFAP (96.3%), and SIDIAP (96.4%). The remaining cases identified in SNDS came from diagnoses (DIA), procedures (PROC) and hospitalization (H). Differently, NHR cases were identified only

through DIA and H, and VID cases were mainly found through PROC and an ER contribution. The absence of MED is associated with the lowest values of cumulative incidence.

*Figure 9. Component Analysis for GD.*



## 10.4 HASHIMOTO THYROIDITIS (HT)

### 10.4.1 Attrition of study population

Incident cases of HT were only identified in BIFAP (n=9,119), SIDIAP (n=2,549), SNDS (n=958) and PEDIANET (n=15). When building up the HT cohort, persons with previous HT diagnosis were excluded. Moreover, the evidence of levothyroxine dispensing within the look-back period was applied as additional exclusion criterion when building up this cohort. The application of this additional criterion had an important impact on the attrition of the study population with HT; for instance, it accounted for 39.3% in BIFAP, 70.4% in SIDIAP, and 64.9% in SNDS of the total persons identified with a HT-related code after the study entry date. Information about levothyroxine use in CPRD, VID and NHR was not available in the data instances used in this study and therefore, were not fit-for-purpose the produce results in this study cohort. See Table 29 below.

*Table 29. Attrition table for the HT cohort*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 17,080 | 8,219 | 7,316 | 15 | 10,241 | 3,894 | 6,498 |
| Disease codes found during lookback | 1,244 | 1,333 | 2,927 | 0 | 479 | 409 | 1,244 |
| Other criteria suggesting the disease is present during lookback | 6,719 | 6,886 | 4,389 | 0 | 7,213 | 2,528 | 5,254 |
| Total cohort of Hashimoto's thyroiditis | 9,119 | NA | NA | 15 | 2,549 | 958 | NA |
| Persons dying before entrance in the follow-up | 88 | 0 | 0 | NR | NR | 9 | 0 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 422 | 0 | 0 | NR | NR | 55 | 0 |
| Persons entering follow-up | 8,609 | NA | NA | 11 | 2,524 | 894 | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.2 Characteristics of the study cohort

Females accounted between 80.0%, and 85.4% of the HT cohort population across data sources. Median age in BIFAP, SIDIAP and SNDS was between 46 and 53-year-old. In PEDIANET, the median age was 11 years.
In BIFAP and SIDIAP, 26.7% and 33.1%, respectively, of the HT cohort did not receive any vaccination during follow-up. This figure goes up to 57.7% in SNDS. See Table 30.

*Table 30. Characteristics of the HT study cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 9,119 | 0 | 0 | 15 | 2,549 | 958 | 0 |
| Female (n/%) | 7,586 (83.2%) | NA | NA | NR | 5,583 (85.4%) | 797 (80.2%) | NA |
| Male (n/%) | 1,533 (16.8%) | NA | NA | NR | 958 (14.6%) | 197 (19.8%) | NA |
| Other (n/%) | 0 (0%) | NA | NA | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Age in year (IQR): PCT 25 | 36 | NA | NA | 8 | 35 | 39 | NA |
| Age in year (IQR): PCT 50 | 48 | NA | NA | 11 | 46 | 53 | NA |
| Age in year (IQR): PCT 75 | 61 | NA | NA | 11.5 | 58 | 68.7 | NA |
| Age in categories (n/%): < 18 | 722 (7.9%) | NA | NA | 15 (100%) | 360 (5.5%) | 40 (4.0%) | NA |
| Age in categories (n/%): 18-59 | 5,913 (64.8%) | NA | NA | 0 (0%) | 4,732 (72.3%) | 569 (57.2%) | NA |
| Age in categories (n/%): > 60 | 2,484 (27.2%) | NA | NA | 0 (0%) | 1449 (22.2%) | 385 (38.7%) | NA |
| Number of persons who started the follow-up | 8,609 (94.4%) | NA | NA | 11 (100%) | 6,241 (95.4%) | 923 (92.9%) | NA |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 27,372 | NA | NA | 25 | 19,599 | 1,788 | NA |
| Number of vaccinations during follow-up (median, IQR) | 2 | NA | NA | 1 | 2 | 0 | NA |
| Number of people with vaccinations (n/%): 0 | 2,432 (26.7%) | NA | NA | < 5 | 2,162 (33.1%) | 574 (57.7%) | NA |
| Number of people with vaccinations (n/%): 1 | 914 (10%) | NA | NA | < 5 | 562 (8.6%) | 127 (12.8%) | NA |
| Number of people with vaccinations (n/%): 2 | 1,288 (14.1%) | NA | NA | < 5 | 986 (15.1%) | 94 (9.5%) | NA |
| Number of people with vaccinations (n/%): 3 or more | 3,975 (43.6%) | NA | NA | < 5 | 2,531 (38.7%) | 128 (12.9%) | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 31. presents comorbidities and medication used during the look-back period. The most prevalent comorbidities among the HT cohort subjects were cancer-related diagnoses (3.4% to 9.1%) and immunocompromised status (2.6% to 6.1%). Antibiotic use was particularly high in SNDS (50.7%), while 22% in SIDIAP and BIFAP. In general, the use of all medications amongst French SNDS HT patients was higher than in BIFAP and SIDIAP. PEDIANET HT study cohort was very small with very small counts of comorbidities or comedications identified.

*Table 31. Comorbidities and comedication in the HT study cohort.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 9,119 | 0 | 0 | 15 | 2,549 | 958 | 0 |
| Immunocompromise status (n/%) | 238 (2.6%) | NA | NA | 0 (0%) | 49 (1.9%) | 58 (6.1%) | NA |
| Malignancy (n/%) | 381 (4.2%) | NA | NA | 0 (0%) | 87 (3.4%) | 87 (6.1%) | NA |
| Hepatitis C (n/%) | 8 (0.1%) | NA | NA | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Sjogren's syndrome (n/%) | 9 (0.1%) | NA | NA | 0 (0%) | < 5 | < 5 | NA |
| Myasthenia gravis (n/%) | 9 (0.1%) | NA | NA | 0 (0%) | 0 (0%) | 5 (0.5%) | NA |
| Pernicious anemia (n/%) | 8 (0.1%) | NA | NA | <5 | <5 | < 5 | NA |
| Autoimmune hepatitis (n/%) | 6 (0.1%) | NA | NA | 0 (0%) | <5 | < 5 | NA |
| Celiac disease (n/%) | 10 (0.1%) | NA | NA | <5 | 6 (0.2%) | < 5 | NA |
| Immunostimulants (n/%) | 0 (0%) | NA | NA | 0 (0%) | 0 (0%) | 7 (0.7%) | NA |
| Analgesics (n/%) | 2,689 (29.5%) | NA | NA | 0 (0%) | 722 (28.3%) | 691(72.1%) | NA |
| Systemic corticosteroids (n/%) | 575 (6.3%) | NA | NA | 0 (0%) | 134 (5.3%) | 283 (29.5%) | NA |
| Antithrombotic agents (n/%) | 849 (9.3%) | NA | NA | 0 (0%) | 154 (6.0%) | 202 (21.1%) | NA |
| Sex hormones (n/%) | 354 (3.9%) | NA | NA | 0 (0%) | 121 (4.7%) | 161 (16.8%) | NA |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 619 (6.8%) | NA | NA | 0 (0%) | 134 (5.3%) | 290 (30.3%) | NA |
| Diabetes medications (n/%) | 559 (6.1%) | NA | NA | 0 (0%) | 93 (3.6%) | 142 (14.8%) | NA |
| Antibiotics (n/%) | 2,019 (22.1%) | NA | NA | <5 | 557 (21.9%) | 468 (50.7%) | NA |
| Antiviral drugs (n/%) | 94 (1.0%) | NA | NA | 0 (0%) | 18 (0.7%) | 35 (3.7%) | NA |
| Antimycotics (n/%) | 93 (1.0%) | NA | NA | 0 (0%) | 19 (0.7%) | 37 (3.9%) | NA |
| Non-steroidal anti-inflammatory drugs (n/%) | 2,107 (23.1%) | NA | NA | 0 (0%) | 677 (26.6%) | NA | NA |
| Drug to treat mental health diseases (n/%) | 1,220 (13.4%) | NA | NA | 0 (0%) | 287 (11.3%) | 180 (18.8%) | NA |
| Lipid lowering drugs (n/%) | 1,026 (11.3%) | NA | NA | 0 (0%) | 182 (7.1%) | 174 (18.2%) | NA |
| Cardiovascular medication (n/%) | 2,110 (23.1%) | NA | NA | 0 (0%) | 439 (17.2%) | 414 (43.2%) | NA |
| Oncologic drugs (n/%) | 78 (0.9%) | NA | NA | 0 (0%) | 18 (0.7%) | 37 (3.9%) | NA |
| Anti-epileptics (n/%) | 466 (5.1%) | NA | NA | 0 (0%) | 115 (4.5%) | 72 (7.5%) | NA |
| Diuretics (n/%) | 0 (0%) | NA | NA | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | NA | NA | 0 (0%) | 0 (0%) | < 5 | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.3 IRs of HT flares

#### 10.4.3.1 IRs of HT flares in the general population

The IR of the first flare episode of HT was 186.5 per 1,000 PY (CI 95% 174.8-198.6) in SIDIAP, 110.6 per 1,000 PY (CI 95% 13.4-399.6) in PEDIANET, 107.5 per 1,000 PY (CI 95% 102.7-112.4) in BIFAP, and 67.8 per 1,000 PY (CI 95% 54.8-82.9) in SNDS (hospital and outpatient diagnoses only). Second and third flares cases were only identified in BIFAP. The IRs of second flares in this data source was 1.8 (CI 95% 0.8-3.5), while the third episode of flares counted less than 5 individuals, causing IR of 151 (CI 95% 3.8-846.2) per 1,000 PY.

*Table 32. Background incidence rate of first, second, and third flare in the cohort of HT, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 9,119 | 0 | 0 | 15 | 2,549 | 958 | 0 |
| Number of persons who started the follow-up | 8,585 | NA | NA | 11 | 2,517 | 890 | NA |
| Number of persons who develop a first flare-up episode | 1,925 | NA | NA | < 5 | 960 | 94 | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 107.5 (102.7-112.4) | NA | NA | 110.6 (13.4-399.6) | 186.5 (174.8-198.6) | 67.8 (54.8-82.9) | NA |
| Number of persons still in the study 90 days after first flare | 1,821 | NA | NA | < 5 | 952 | 81 | NA |
| Number of persons who develop a second flare-up episode | 8 | NA | NA | 0 | 0 | 0 | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 1.8 (0.8-3.5) | NA | NA | 0 (0-1,096.3) | 0 (0-1.8) | 0 (0-35.7) | NA |
| Number of persons still in the study 90 days after second flare | 7 | NA | NA | NA | NA | NA | NA |
| Number of persons who develop a third flare-up episode | < 5 | NA | NA | NA | NA | NA | NA |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 151.9 (3.8-846.2) | NA | NA | NA | NA | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.3.2 IRs of HT flares stratified per age categories

Most of the people experiencing a first episode of HT flares were adults 18-59 years old, followed by people ≥60 years old, and then children and adolescents <18 years old (see Table 33). Across age categories, cases of first flares are observed in BIFAP, SIDIAP and SNDS, while PEDIANET shows <5 only for 0-17-year-olds (paediatric database). IRs of the first episodes was higher in 0-17-year-olds in SIDIAP. In BIFAP and SNDS, the first flare episodes were higher in the 18-59-year-old category, with rates of 114.6 and 195.7 per 1,000 PY, respectively. In those ≥60-year-old, incidence of the first rate episode ranged from 6.51 (SNDS) to 146.2 (SIDIAP) per 1,000 PY.

For the second flare episode, only BIFAP reported few cases across age categories: <5 for 0-17-year-olds (IR = 3.8 per 1000 PY), 6 for 18-59-year-olds (IR = 1.8 per 1000 PY), and <5 for ≥60-year-olds (IR = 1.0 per 1000 PY). Regarding the third episode, BIFAP reported <5 cases for 18-59-year-olds (IR = 260.1 per 1000 PY).

*Table 33 Background incidence rate of first, second, and third flare in the HT cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 133 | NA | NA | < 5 | 45 | < 5 | NA |
| Number of persons who develop a first flare-up episode | 18-59 | 1384 | NA | NA | | 744 | 57 | NA |
| Number of persons who develop a first flare-up episode | 60+ | 408 | NA | NA | | 171 | 35 | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 108.4 (90.8-128.5) | NA | NA | 110.6 (13.4-399.6) | 253.9 (185.2-339.7) | 47.1 (5.7-170.3) | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 114.6 (108.7-120.8) | NA | NA | NA | 195.7 (181.9-210.3) | 70.6 (53.5-91.5) | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 88.4 (80.1-97.4) | NA | NA | NA | 146.2 (125.1-169.8) | 65.1 (45.4-90.6) | NA |
| Number of persons still in the study 90 days after first flare | 0-17 | 123 | NA | NA | < 5 | 40 | < 5 | NA |
| Number of persons still in the study 90 days after first flare | 18-59 | 1349 | NA | NA | | 749 | 51 | NA |
| Number of persons still in the study 90 days after first flare | 60+ | 507 | NA | NA | | 211 | 31 | NA |
| Number of persons who develop a second flare-up episode | 0-17 | < 5 | NA | NA | 0 | 0 | 0 | NA |
| Number of persons who develop a second flare-up episode | 18-59 | 6 | NA | NA | | 0 | 0 | NA |
| Number of persons who develop a second flare-up episode | 60+ | < 5 | NA | NA | | 0 | 0 | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 3.8 (0.1-21) | NA | NA | 0 (0-1096.3) | 0 (0-59.7) | 0 (0-2705.5) | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 1.8 (0.7-4) | NA | NA | NA | 0 (0-2.3) | 0 (0-53.6) | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 1 (0-5.6) | NA | NA | NA | 0 (0-9.4) | 0 (0-111.5) | NA |
| Number of persons still in the study 90 days after second flare | 0-17 | < 5 | NA | NA | | | | NA |
| Number of persons still in the study 90 days after second flare | 18-59 | 6 | NA | NA | | | | NA |
| Number of persons still in the study 90 days after second flare | 60+ | < 5 | NA | NA | | | | NA |

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | 0-17 | 0 | NA | NA | | | | NA |
| Number of persons who develop a third flare-up episode | 18-59 | < 5 | NA | NA | | | | NA |
| Number of persons who develop a third flare-up episode | 60+ | 0 | NA | NA | | | | NA |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 0 (0-1879.2) | NA | NA | NA | NA | NA | NA |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 260.1 (6.6-1449.5) | NA | NA | NA | NA | NA | NA |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 0 (0-4744.2) | NA | NA | NA | NA | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.3.3 IRs of HT flares stratified per gender

Across BIFAP, SIDIAP and SNDS, the incidence rate of the first flare episode was higher in females than males, although the confidence intervals overlap, see Table 34. PEDIANET only reported <5 cases across females (IR = 137.9 per 1000 PY), with no cases for males. This is in line with reported evidence about HT being a disease that mainly affects females (41,42). Few cases of second flares were observed in BIFAP, 7 in females (IR = 1.8 per 1000 PY) and <5 in males (IR = 1.4 per 1000 PY), as well as few cases of third flares with <5 in females (IR = 161.3 per 1000 PY) and no cases in males.

*Table 34 Background incidence rate of first, second, and third flare in the HT cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 1631 | | | < 5 | 841 | 80 | |
| Number of persons who develop a first flare-up episode | M | 294 | | | 0 | 119 | 14 | |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 108.3 (103.1-113.7) | NA | NA | 137.9 (16.7-813.2) | 192.8 (180-206.3) | 70.2 (55.6-87.3) | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 103.1 (97.1-115.6) | NA | NA | 0 (0-1033.3) | 151.4 (125.4-181.2) | 56.8 (31-95.3) | NA |
| Number of persons still in the study 90 days after first flare | F | 1936 | | | < 5 | 1213 | 83 | |
| Number of persons still in the study 90 days after first flare | M | 281 | | | | 119 | 12 | |
| Number of persons who develop a second flare-up episode | F | 7 | | | 0 | 0 | 0 | |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a second flare-up episode | M | < 5 | | | | 0 | 0 | |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 1.8 (0.7-3.8) | NA | NA | 0 (0-1096.3) | 0 (0-2.1) | 0 (0-41.5) | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 1.4 (0-7.8) | NA | NA | NA | 0 (0-14) | 0 (0-256.3) | NA |
| Number of persons still in the study 90 days after second flare | F | 6 | | | | | | |
| Number of persons still in the study 90 days after second flare | M | < 5 | | | | | | |
| Number of persons who develop a third flare-up episode | F | < 5 | | | | | | |
| Number of persons who develop a third flare-up episode | M | 0 | | | | | | |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 161.3 (4.1-898.5) | NA | NA | NA | NA | NA | NA |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 0 (0-9624) | NA | NA | NA | NA | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.3.4 IRs of HT flares in pregnant population

SNDS and BIFAP could not run the pregnancy algorithm, therefore no sub analysis was conducted. In SIDIAP 24 pregnant people were identified, very few (<5) had a first flare episode leading to an IR of 265.5 per 1,000 PY (CI 95% 54.7-775.6), see Table 35.

*Table 35. Background incidence rate in the pregnant population of first, second, and third flare in the cohort of HT, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | NA | 24 | NA | NA |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | NA | < 5 | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | 265.5 (54.7-775.6) | NA | NA |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | NA | 13 | NA | NA |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | NA | 0 | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | 0 (0-553.3) | NA | NA |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | NA | NA | NA | NA |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | NA | NA | NA | NA |

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | NA | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.4.4 Six- and twelve-months cumulative incidence of flares of HT

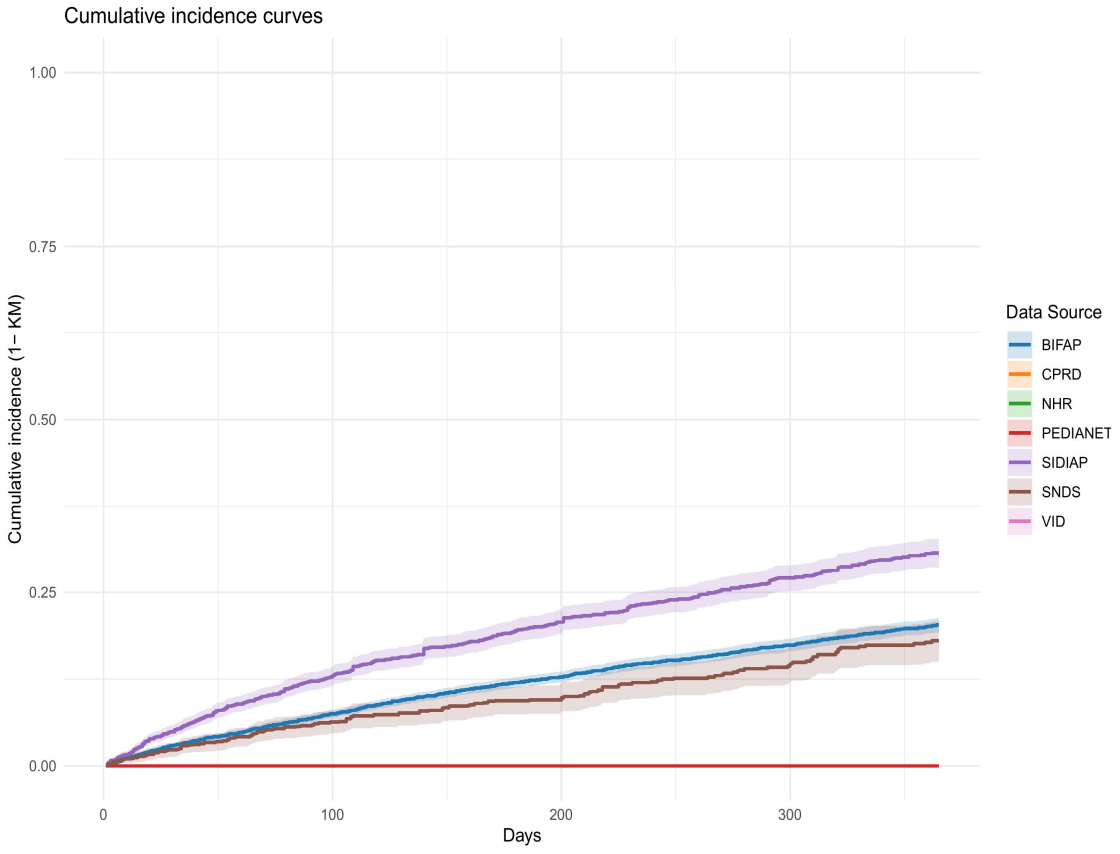
The six months risk of a HT flare was 19.5% in SIDIAP, 12.0% in BIFAP, 0% in PEDIANET and 9.4% in SNDS. The 12-months risk was 30.8% in SIDIAP, 20.3% in BIFAP and 18.0% in SNDS, whereas it remained zero in PEDIANET. In Figure 10, the cumulative incidence curve of HT is depicted.

*Table 36 Six- and twelve-months cumulative incidence of flares of Hashimoto's thyroiditis, with 95% confidence intervals.*

| Days | BIFAP | SIDIAP | PEDIANET | SNDS |
|---|---|---|---|---|
| 180 | 0.12 (0.113-0.128) | 0.195 (0.178-0.211) | 0 (0-0) | 0.094 (0.074-0.114) |
| 365 | 0.203 (0.192-0.213) | 0.308 (0.287-0.328) | 0 (0-0) | 0.18 (0.15-0.208) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 10. Cumulative incidence curve HT.*

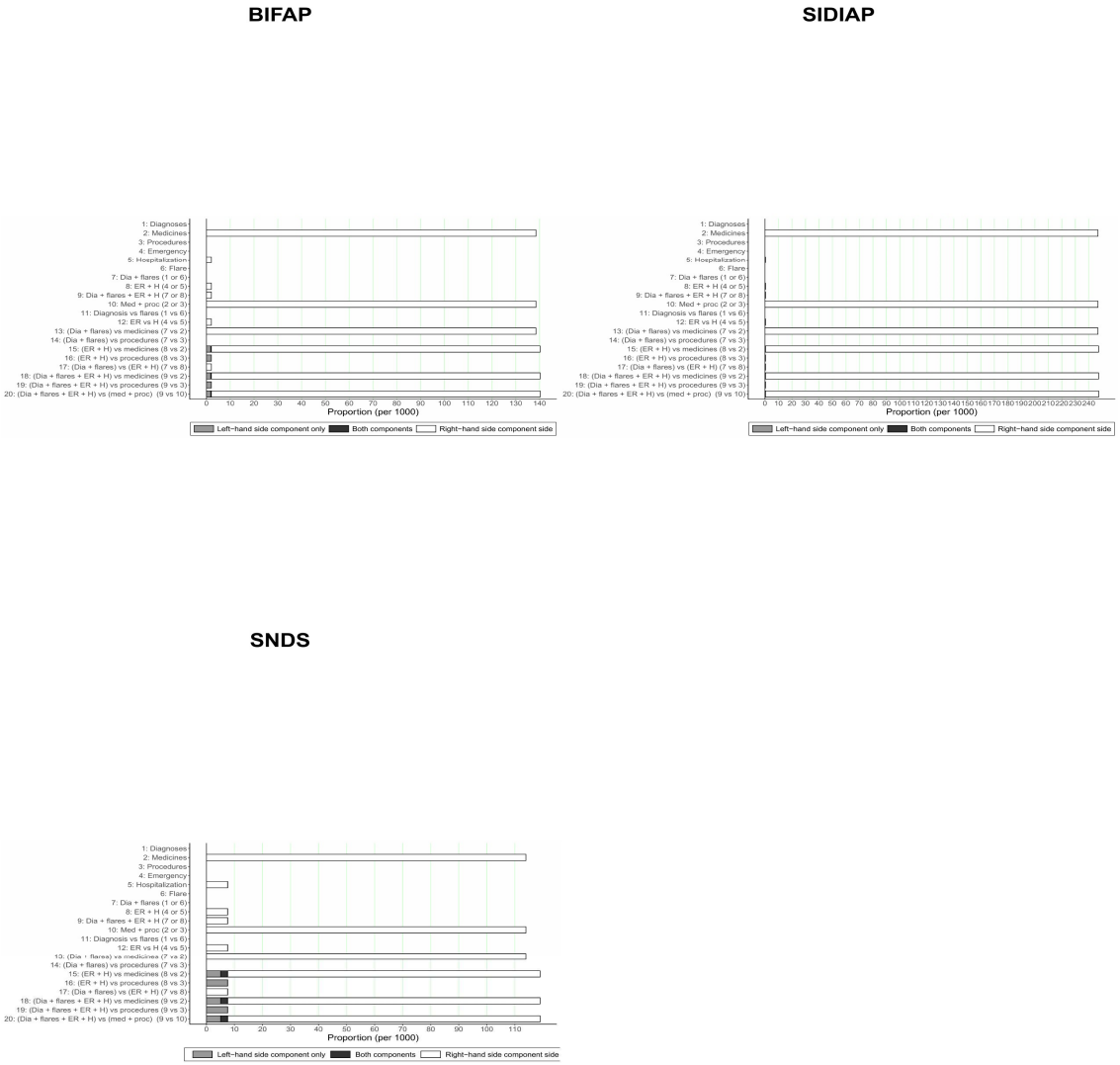



### 10.4.5 Other analyses

#### 10.4.5.1 Component analysis

Considering the components used to identify HT flares (see Figure 11), MED accounted for >95% of the 12-month cumulative incidence of the first episode in the three data sources where the component analysis could be performed. The remaining cases were identified from H.

*Figure 11. Component Analysis for HT.*



## 10.5 MULTIPLE SCLEROSIS (MS)

### 10.5.1 Attrition of study population

In CPRD, 720 subjects entered the MS disease cohort, 99% (n=713) of them started the follow up 90 days later. In VID, after application of the exclusion criteria 186 subjects with MS remained in the cohort, 93.5% (n=174) of them started the follow up 90 days later. In the French database SNDS, 2,860 MS patients became part of the study cohort, 91.7% (n=2,622) of them started the follow-up. In BIFAP-ES, 6,555 individuals entered the cohort and 6,207 (94.7%) started the follow up. No individuals with MS were identified in PEDIANET, SIDIAP and NHR. See Table 37 below.

*Table 37. Characteristics of the study MS cohort.*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking requiring data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 12,020 | 27,454 | 5,465 | 1 | 5,489 | 8,670 | 19,168 |
| Disease codes found during lookback | 5,465 | 11,519 | 3,036 | 0 | 1,158 | 5,767 | 13,229 |
| Other criteria suggesting the disease is present during lookback | 0 | 15,215 | 2,243 | < 5 | 4,331 | 43 | 5,939 |
| Total cohort of Multiple sclerosis | 6,555 | 720 | 186 | NA | NA | 2,860 | NA |
| Persons dying before entrance in the follow-up | 59 | 0 | NR | 0 | 0 | 36 | 0 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 289 | 7 | NR | 0 | 0 | 202 | 0 |
| Persons entering follow-up | 6,207 | 713 | 174 | NA | NA | 2,622 | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.5.2 Characteristics of the study cohort

The MS cohort who started follow up 90 days after diagnoses, across databases comprised 9,716 subjects. The total follow-up time was 296 PY in VID, 5,096 PY in SNDS, 2,873 PY in CPRD, 20,201 PY in BIFAP, while in PEDIANET, SIDIAP and NHR there were no incident MS cases. Across data sources, between 65.5 to 76.9% of the MS cohort were

females. The male-to-female sex ratio in MS incident cases across databases was 30 males to every 100 females. The median age (interquartile range 50) was between 40- to 46-year-old across data sources. Data about median age of people with MS diagnosis and female preponderance are in line with publications about general population affected by such disease (43,44). The percentage of MS persons with at least 3 vaccinations during follow-up ranged from 8.5% in CPRD to 12.9% in VID. See Table 38**.**

*Table 38. Characteristics of the study MS cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,555 | 720 | 186 | 0 | 0 | 2,860 | 0 |
| Female (n/%) | 4,292 (65.5%) | 541 (75.1%) | 143 (76.9%) | 0 (NA%) | 0 (NA%) | 1,954 (68.3%) | 0 (NA%) |
| Male (n/%) | 2,263 (34.5%) | 179 (24.9%) | 43 (23.1%) | 0 (NA%) | 0 (NA%) | 906 (31.7%) | 0 (NA%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | NA | 0 (0%) | NA |
| Age in year (IQR): PCT 25 | 31.00 | 36.00 | 32.25 | NA | NA | 31.00 | NA |
| Age in year (IQR): PCT 50 | 40 | 46 | 41 | NA | NA | 43 | NA |
| Age in year (IQR): PCT 75 | 51 | 53 | 50 | NA | NA | 55 | NA |
| Age in categories (n/%): < 18 | 461 (7%) | 8 (1.1%) | < 5 | NA | NA | 42 (1.5%) | NA |
| Age in categories (n/%): 18-59 | 5,335 (81.4%) | 639 (88.8%) | 169 (90.9%) | 0 (NA%) | 0 (NA%) | 2,292 (80.1%) | 0 (NA%) |
| Age in categories (n/%): > 60 | 759 (11.6%) | 73 (10.1%) | 13 (7%) | 0 (NA%) | 0 (NA%) | 526 (18.4%) | 0 (NA%) |
| Number of persons who started the follow-up | 6,207 (94.7%) | 713 (99%) | 174 (93.5%) | 0 (NA%) | 0 (NA%) | 2,622 (91.7%) | 0 (NA%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 20,201 | 2,873 | 296 | 0 | 0 | 5,096 | 0 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 0 | NA | NA | 0 | NA |
| Number of people with vaccinations (n/%): 0 | 1,421 (21.7%) | 515 (71.5%) | 99 (53.2%) | 0 (NA%) | 0 (NA%) | 1,646 (57.6%) | 0 (NA%) |
| Number of people with vaccinations (n/%): 1 | 647 (9.9%) | 87 (12.1%) | 32 (17.2%) | 0 (NA%) | 0 (NA%) | 377 (13.2%) | 0 (NA%) |
| Number of people with vaccinations (n/%): 2 | 864 (13.2%) | 50 (6.9%) | 19 (10.2%) | 0 (NA%) | 0 (NA%) | 264 (9.2%) | 0 (NA%) |
| Number of people with vaccinations (n/%): 3 or more | 3,275 (50%) | 61 (8.5%) | 24 (12.9%) | 0 (NA%) | 0 (NA%) | 335 (11.7%) | 0 (NA%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 39 describes comorbidities at baseline of MS patients in BIFAP, VID, SNDS and CPRD. All MS patients had a code or drug implying an immunocompromised status during the look-back period. Cancer diagnosis was identified in 102 individuals in BIFAP, 94 individuals in SNDS, 9 individuals in CPRD and <5 individuals in VID.
SNDS reports the highest prevalence of drug use across most therapeutic groups, with some exceptions. NSAIDs were observed in 26.5% in BIFAP, 14% of CPRD and 38.7% of the VID cohort, whereas none was identified in SNDS claims data. Moreover, drugs to treat mental health diseases, lipid lowering drugs, cardiovascular medications, and anti-epileptics were slightly higher in CPRD and VID than in BIFAP and SNDS. Additionally, anti-epileptics were almost double in VID than in BIFAP and CPRD.

*Table 39 Comorbidities in the study cohort with MS*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,555 | 720 | 186 | 0 | 0 | 2,860 | 0 |
| Immunocompromise status (n/%) | 157 (2.4%) | 10 (1.4%) | 30 (16.1%) | 0 (0%) | 0 (0%) | 181 (6.3%) | 0 (0%) |
| Malignancy (n/%) | 102 (1.6%) | 9 (1.2%) | < 5 | 0 (0%) | 0 (0%) | 94 (3.3%) | 0 (0%) |
| Influenza (n/%) | 373 (5.7%) | < 5 | < 5 | 0 (0%) | 0 (0%) | < 5 | 0 (0%) |
| Obesity (n/%) | 80 (1.2%) | < 5 | 5 (2.7%) | 0 (0%) | 0 (0%) | 72 (2.5%) | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 464 (7.1%) | 69 (9.6%) | 44 (23.7%) | 0 (0%) | 0 (0%) | 929 (32.5%) | 0 (0%) |
| Immunostimulants (n/%) | 0 (0%) | < 5 | 6 (3.2%) | 0 (0%) | 0 (0%) | 7 (0.2%) | 0 (0%) |
| Analgesics (n/%) | 1,810 (27.6%) | 244 (33.9%) | 81 (43.5%) | 0 (0%) | 0 (0%) | 1,969 (68.8%) | 0 (0%) |
| Systemic corticosteroids (n/%) | 423 (6.5%) | 64 (8.9%) | 19 (10.2%) | 0 (0%) | 0 (0%) | 868 (30.3%) | 0 (0%) |
| Antithrombotic agents (n/%) | 483 (7.4%) | 44 (6.1%) | 16 (8.6%) | 0 (0%) | 0 (0%) | 349 (12.2%) | 0 (0%) |
| Sex hormones (n/%) | 369 (5.6%) | 140 (19.4%) | 8 (4.3%) | 0 (0%) | 0 (0%) | 563 (19.7%) | 0 (0%) |
| Diabetes medications (n/%) | 242 (3.7%) | 30 (4.2%) | 5 (2.7%) | 0 (0%) | 0 (0%) | 126 (4.4%) | 0 (0%) |
| Antibiotics (n/%) | 1,286 (19.6%) | 232 (32.2%) | 59 (31.7%) | 0 (0%) | 0 (0%) | 1,283 (44.9%) | 0 (0%) |
| Antiviral drugs (n/%) | 71 (1.1%) | 11 (1.5%) | 6 (3.2%) | 0 (0%) | 0 (0%) | 120 (4.2%) | 0 (0%) |
| Antimycotics (n/%) | 63 (1%) | 11 (1.5%) | 0 (0%) | 0 (0%) | 0 (0%) | 83 (2.9%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 1,737 (26.5%) | 104 (14.4%) | 72 (38.7%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Drug to treat mental health diseases (n/%) | 1,058 (16.1%) | 306 (42.5%) | 53 (28.5%) | 0 (0%) | 0 (0%) | 590 (20.6%) | 0 (0%) |
| Lipid lowering drugs (n/%) | 564 (8.6%) | 69 (9.6%) | 19 (10.2%) | 0 (0%) | 0 (0%) | 250 (8.7%) | 0 (0%) |
| Cardiovascular medication (n/%) | 1,107 (16.9%) | 154 (21.4%) | 30 (16.1%) | 0 (0%) | 0 (0%) | 677 (23.7%) | 0 (0%) |
| Oncologic drugs (n/%) | 37 (0.6%) | 9 (1.2%) | < 5 | 0 (0%) | 0 (0%) | 58 (2%) | 0 (0%) |
| Anti-epileptics (n/%) | 638 (9.7%) | 44 (6.1%) | 33 (17.7%) | 0 (0%) | 0 (0%) | 397 (13.9%) | 0 (0%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 15 (0.5%) | 0 (0%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.5.3 IRs of MS flares

#### 10.5.3.1 IRs of MS flares in the general population

In BIFAP, 394 individuals developed a first MS flare, with IRs of 25 per 1,000 PY (CI95% 22.6-27.6). In CPRD, 527 individuals developed a first MS flare, with IRs of 400.4 per 1,000 PY (CI95% 367-436.1). In VID, 67 people developed a first flare, leading to an IR of 396.5 per 1,000 PY (CI95% 307.3-503.5). In SNDS, 835 subjects had a first flare, leading to an IR of first flare-up episode of 256.5.4/1,000 PY (CI 95% 239.4-274.5). IRs of second flare were much lower in all data sources compared to the first flare incidence except in BIFAP with IRs of 169.2 per 1,000 PY (CI95% 136.7-207.1). IRs per 1,000 PY were 81.3 in CPRD, 91.9 in VID, and 524.3 in SNDS . IRs of third flare were even lower in CPRD and VID, but it increased in BIFAP and SNDS compared to the second episode with an IRs per 1,000PY of 701.5 (see Table 40).

*Table 40 Background incidence rate of first, second, and third flare in the MS cohort, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,555 | 720 | 186 | 0 | 0 | 2,860 | 0 |
| | | | | | | | |
| Number of flares before entering follow-up | 266 | 69 | 76 | 0 | 0 | 927 | 0 |
| Number of persons who develop a first flare-up episode | 394 | 527 | 67 | NA | NA | 835 | NA |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 25 (22.6-27.6) | 400.4 (367-436.1) | 396.5 (307.3-503.5) | NA (NA-NA) | NA (NA-NA) | 256.5 (239.4-274.5) | NA (NA-NA) |
| Number of persons still in the study 90 days after first flare | 364 | 505 | 59 | NA | NA | 716 | NA |
| Number of persons who develop a second flare-up episode | 94 | 92 | 6 | NA | NA | 325 | NA |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 169.2 (136.7-207.1) | 81.3 (65.5-99.7) | 91.9 (33.7-200.1) | NA (NA-NA) | NA (NA-NA) | 524.3 (468.8-584.5) | NA (NA-NA) |
| Number of persons still in the study 90 days after second flare | 83 | 84 | 5 | NA | NA | 254 | NA |
| Number of persons who develop a third flare-up episode | 38 | 9 | 0 | NA | NA | 148 | NA |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | 418 (295.8-573.7) | 64.2 (29.4-121.9) | 0 (0-859.3) | NA (NA-NA) | NA (NA-NA) | 1115.9 (943.4-1310.9) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.5.3.2 IRs of MS flares stratified per age categories

Most of the people experiencing flares of MS were adults ≥ 18 years old, followed by ≥60 years old individuals. Overall, the incidence of flares increased from the first episode to the second one for BIFAP and SNDS, and decrease for CPRD and VID across age categories. For the 0-17-year-old category, the IRs of the first flare ranged from 9.6 (BIFAP) to 1786.1 (VID) per 1000 PY, while the IRs of the second flare episodes span from 0 (CPRD and VID) to 92.4 (BIFAP) and 792.5 (SNDS) per 1000 PY. For the 18–59-year-old category, the IRs per 1000 PY of the first flare ranged from 27 (BIFAP) to

426.7 (CPRD), while the rates of the second flare episodes were from 89.1 (CPRD) to 518 (SNDS). For the ≥60-year-old category, the IRs per 1000 PY ranged from 18 (BIFAP) to 359.3 (VID) for the first flare, while IRs ranged from 33.8 (CPRD) to 531.5 (SNDS) for the second flare episodes.
Regarding the third flares' episodes, only a few cases were found in BIFAP, CPRD and SNDS, while no cases were found in VID. For the 0-17-year-old category, no episodes in BIFAP, <5 episodes in SNDS with the IRs of 960.3 per 1000 PY. For the 18–59-year-old category, the IRs per 1000 PY were 69.3 in CPRD, 413.1 in BIFAP, and 1110.1 in SNDS for the third flare. For the ≥60-year-old category, <5 episodes in BIFAP and 20 in SNDS, with IRs of 587 and 1183.4 per 1000 PY, respectively.

*Table 41 Background incidence rate of first, second, and third flare in the MS cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 9 | < 5 | < 5 | | | 16 | |
| Number of persons who develop a first flare-up episode | 18-59 | 354 | 473 | 59 | | | 725 | |
| Number of persons who develop a first flare-up episode | 60+ | 31 | 51 | 6 | | | 94 | |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 9.6 (4.4-18.3) | 1351.1 (278.6-3948.5) | 1786.1 (216.3-6451.9) | NA (NA-NA) | NA (NA-NA) | 565.1 (323-917.6) | NA (NA-NA) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 27 (24.3-30) | 426.7 (389.1-467) | 390.3 (297.1-503.4) | NA (NA-NA) | NA (NA-NA) | 291 (270.2-313) | NA (NA-NA) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 18 (12.2-25.5) | 248.3 (184.9-326.4) | 359.3 (131.9-782.1) | NA (NA-NA) | NA (NA-NA) | 127.7 (103.2-156.3) | NA (NA-NA) |
| Number of persons still in the study 90 days after first flare | 0-17 | 7 | < 5 | < 5 | | | 13 | |
| Number of persons still in the study 90 days after first flare | 18-59 | 332 | 454 | 51 | | | 614 | |
| Number of persons still in the study 90 days after first flare | 60+ | 37 | 72 | 7 | | | 103 | |
| Number of persons who develop a second flare-up episode | 0-17 | < 5 | 0 | 0 | | | 8 | |
| Number of persons who develop a second flare-up episode | 18-59 | 87 | 87 | 6 | | | 272 | |
| Number of persons who develop a second flare-up episode | 60+ | 6 | 5 | 0 | | | 45 | |
| IR of second flare-up episode, per 1,000 PY PY (CI 95%) | 0-17 | 92.4 (2.3-514.5) | 0 (0-534.5) | 0 (0-1513.9) | NA (NA-NA) | NA (NA-NA) | 792.5 (342.2-1561.6) | NA (NA-NA) |
| IR of second flare-up episode, per 1,000 PY PY (CI 95%) | 18-59 | 173 (138.6-213.4) | 89.1 (71.4-109.9) | 106.9 (39.2-232.6) | NA (NA-NA) | NA (NA-NA) | 518 (458.2-583.3) | NA (NA-NA) |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| IR of second flare-up episode, per 1,000 PY PY (CI 95%) | 60+ | 143.4 (52.6-312.2) | 33.8 (11-78.8) | 0 (0-552) | NA (NA-NA) | NA (NA-NA) | 531.5 (387.7-711.1) | NA (NA-NA) |
| Number of persons still in the study 90 days after second flare | 0-17 | < 5 | | | | | 6 | |
| Number of persons still in the study 90 days after second flare | 18-59 | 76 | 79 | 5 | | | 215 | |
| Number of persons still in the study 90 days after second flare | 60+ | 7 | 6 | | | | 33 | |
| Number of persons who develop a third flare-up episode | 0-17 | 0 | | | | | < 5 | |
| Number of persons who develop a third flare-up episode | 18-59 | 34 | 9 | 0 | | | 125 | |
| Number of persons who develop a third flare-up episode | 60+ | < 5 | 0 | | | | 20 | |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | 0-17 | 0 (0-2063.3) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 960.3 (198-2806.5) | NA (NA-NA) |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | 18-59 | 413.1 (286.1-577.2) | 69.3 (31.7-131.6) | 0 (0-859.3) | NA (NA-NA) | NA (NA-NA) | 1110.1 (924.1-1322.7) | NA (NA-NA) |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | 60+ | 587 (159.9-1502.9) | 0 (0-357.5) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | 1183.4 (722.8-1827.6) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.5.3.3 IRs of MS flares stratified per gender

Across BIFAP, CPRD, VID, and SNDS, the number of females experiencing a first episode of MS flares was higher than that of males, as shown in Table 42. This is in line with the reported evidence about MS being a disease that mainly affects females (45).

The IRs per 1000 PY of first MS flares were observed to be higher for females rather than males in all data sources BIFAP (females: 26; males: 23), SNDS (females: 263; males: 242.1), and CPRD (females: 406.6; males: 382.7), except for VID (females: 374.1; males: 473.8).

The number of cases and the IRs per 1000 PY of second MS flares were lower than the first episodes and higher for females in CPRD (females: 86.8; males: 63.6), while the opposite was observed in BIFAP (females: 167.8; males: 172.1) and SNDS (females: 476.4; males: 674.8). Only <5 cases of second flares were observed VID for both females and males.

The number of cases of third MS flares was lower than in the first and second episodes, with only 9 cases in the female group for CPRD (IR = 75.3 per 1000 PY), while IRs per 1,000 PY were higher than second flares and for females in BIFAP (females: 483.6; males 323) and higher than second flares and for males in SNDS (females: 1039.9; males: 1302.7).

*Table 42 Background incidence rate of first, second, and third flare in the MS cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 267 | 397 | 49 | | | 589 | |
| Number of persons who develop a first flare-up episode | M | 127 | 130 | 18 | | | 246 | |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 26 (23-29.4) | 406.6 (367.6-448.7) | 374.1 (276.7-494.5) | NA (NA-NA) | NA (NA-NA) | 263 (242.2-285.1) | NA (NA-NA) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 23 (19.2-27.3) | 382.7 (319.7-454.4) | 473.8 (280.8-748.8) | NA (NA-NA) | NA (NA-NA) | 242.1 (212.8-274.3) | NA (NA-NA) |
| Number of persons still in the study 90 days after first flare | F | 244 | 382 | 42 | | | 512 | |
| Number of persons still in the study 90 days after first flare | M | 120 | 123 | 17 | | | 204 | |
| Number of persons who develop a second flare-up episode | F | 62 | 75 | < 5 | | | 224 | |
| Number of persons who develop a second flare-up episode | M | 32 | 17 | < 5 | | | 101 | |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 167.8 (128.6-215.1) | 86.8 (68.2-108.8) | 60.5 (12.5-176.9) | NA (NA-NA) | NA (NA-NA) | 476.4 (416-543) | NA (NA-NA) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 172.1 (117.7-243) | 63.6 (37.1-101.9) | 190.9 (39.4-557.9) | NA (NA-NA) | NA (NA-NA) | 674.8 (549.6-820) | NA (NA-NA) |
| Number of persons still in the study 90 days after second flare | F | 54 | 68 | < 5 | | | 170 | |
| Number of persons still in the study 90 days after second flare | M | 29 | 16 | < 5 | | | 84 | |
| Number of persons who develop a third flare-up episode | F | 26 | 9 | 0 | | | 98 | |
| Number of persons who develop a third flare-up episode | M | 12 | 0 | 0 | | | 50 | |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 483.6 (315.9-708.6) | 75.3 (34.5-143) | 0 (0-2347.3) | NA (NA-NA) | NA (NA-NA) | 1039.9 (844.2-1267.3) | NA (NA-NA) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 323 (166.9-564.2) | 0 (0-178.3) | 0 (0-1355.5) | NA (NA-NA) | NA (NA-NA) | 1302.7 (966.9-1717.4) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.5.3.4 IRs of MS flares in pregnant population

Only VID identified 11 pregnant women who had a pregnancy after the start of follow-up for the MS cohort. The IR per 1,000 PY of the first MS flare among pregnant people in VID was 0 (CI 95% 0-992.2) but with 0observed events. <5 pregnant women did also

experience a second and third flare episode. BIFAP, CPRD, PEDIANET and SNDS did not run the pregnancy algorithm. See Table 43 below.

*Table 43. Background IR in pregnant population of first, second, and third flare in the MS cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO | Cohort characteristics |
|---|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 11 | NA | NA | NA | NA |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 0 | NA | NA | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA (NA-NA) | NA (NA-NA) | 0 (0-992.2) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | < 5 | NA | NA | NA | NA |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | NA | NA | NA | NA |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA (NA-NA) | NA (NA-NA) | 1714.8 (43.4-9554.2) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | < 5 | NA | NA | NA | NA |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | 0 | NA | NA | NA | NA |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA (NA-NA) | NA (NA-NA) | 0 (0-16431.3) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) | NA (NA-NA) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.5.4 Six- and twelve-months cumulative incidence of flares of MS

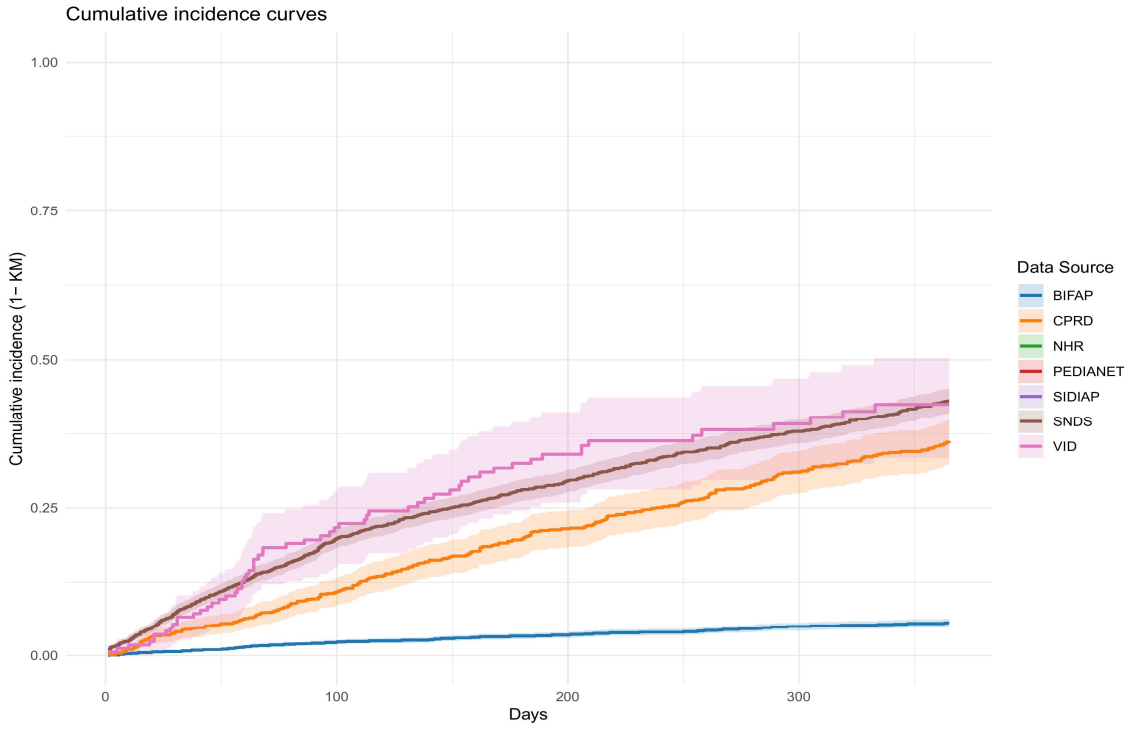
Table 44 shows the 6- and 12-months cumulative incidence of the first flare of MS. The 6-month risk of a first flare in MS patients was 3.3% for VID, 32.5% for BIFAP, 28.1% for SNDS, and 19.8% for CPRD. The 1-year risk of incurring an MS flare was 5.6% in VID, 42.5% in BIFAP, 43.1% in SNDS and 36.3% in CPRD.
The cumulative incidence curve is represented in Figure 12.

*Table 44 Six- and twelve-months cumulative incidence of flares of MS (95% confidence interval)*

| Days | VID-ES | BIFAP-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|
| 180 | 0.033 (0.028-0.038) | 0.325 (0.245-0.395) | 0.281 (0.262-0.298) | 0.198 (0.167-0.227) |
| 365 | 0.056 (0.049-0.063) | 0.425 (0.334-0.503) | 0.431 (0.409-0.451) | 0.363 (0.324-0.399) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 12. Cumulative incidence curve MS.*




### 10.5.5 Other analyses

#### 10.5.5.1 Component analysis

Considering the components used to identify MS flares (see Figure 13), MED accounted for 74.1%, 85.5% and 100% of the 12-month cumulative incidence of the first episode in SNDS, VID and CPRD, respectively, while almost the totality of MS flares in BIFAP were due to H. The remaining cases for VID and SNDS were identified from ER and H, respectively. The overlapping of MED and ER components in VID was 9.7% while MED and H in SNDS was 26.4%.

*Figure 13. Component Analysis of MS.*

## 10.6 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

### 10.6.1 Attrition of study population

Application of exclusion criteria resulted in 6,261 subjects with new SLE identified in BIFAP, with 94.3% (n=5,902) starting the follow-up after 90 days from the first SLE diagnosis. In CPRD, 5,949 SLE subjects entered the disease cohort, 95.9% (n=5,706) of them started the follow up 90 days after the diagnosis. In VID, application of exclusion criteria resulted in a cohort of 3,899 new SLE subjects, 93.8% (n=3,659) of them started the follow up. In SIDIAP, 6,213 subjects entered the SLE cohort, and 94.4% (n=5,863) of them started the follow up 90 days after. In the French database SNDS, 1,901 SLE patients became part of the study cohort, 90.7% (n=1,759) of them started the follow-up. In NHR, 2,169 subjects entered the SLE incident cohort, and 95.3% (n=2,067) started the follow up. Finally, in the Italian PEDIANET database (paediatric population), there were no cases identified. See Table 45 below.

*Table 45 Characteristics of the study SLE cohort*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 10,184 | 9,195 | 7,762 | 0 | 7,817 | 3,521 | 5,552 |
| Disease codes found during lookback | 3,923 | 3,246 | 3,863 | 0 | 1,604 | 1,620 | 3,383 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Systemic lupus erythematosus | 6,261 | 5,949 | 3,899 | NA | 6,213 | 1,901 | 2,169 |
| Persons dying before entrance in the follow-up | 98 | 18 | 38 | 0 | 68 | 35 | 25 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 261 | 225 | 202 | 0 | 282 | 107 | 77 |
| Persons entering follow-up | 5,902 | 5,706 | 3,659 | NA | 5,863 | 1,759 | 2,067 |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.2 Characteristics of the study cohort

The total SLE cohort who started the follow up across databases comprised 24,956 persons. The total follow-up time ranged between 3,385 PY in SNDS to 19,701 PY in CPRD, while in PEDIANET there were no observed cases. Across data sources, between 76 to 89% of the cohort population were females. The median age was between 47- to 52-year-old across data sources, except for PEDIANET (not available). Data about median age of people with SLE diagnosis and female preponderance are in line with other publications about SLE (46–48). The percentage of people with at least 3 vaccinations during follow-up ranged from 8% in CPRD to 63.7% in NHR. See Table 46**.**

*Table 46 Characteristics of the study SLE cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,261 | 5,949 | 3,899 | 0 | 6,213 | 1,901 | 2,169 |
| Female (n/%) | 4,840 (77.3%) | 5,321 (89.4%) | 3,171 (81.3%) | NA | 5,075 (81.7%) | 1,561 (82.1%) | 1,652 (76.2%) |
| Male (n/%) | 1,421 (22.7%) | 628 (10.6%) | 728 (18.7%) | NA | 1,138 (18.3%) | 340 (17.9%) | 517 (23.8%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 39 | 38 | 42 | NA | 40 | 34 | 36 |
| Age in year (IQR): PCT 50 | 52 | 50 | 52 | NA | 52 | 47 | 52 |
| Age in year (IQR): PCT 75 | 67 | 62 | 64 | NA | 65 | 63 | 67 |
| Age in categories (n/%): < 18 | 289 (4.6%) | 166 (2.8%) | 96 (2.5%) | NA | 120 (1.9%) | 64 (3.4%) | 99 (4.6%) |
| Age in categories (n/%): 18-59 | 3,694 (59%) | 3,970 (66.7%) | 2,502 (64.2%) | NA | 3,922 (63.1%) | 1,289 (67.8%) | 1,268 (58.5%) |
| Age in categories (n/%): > 60 | 2,278 (36.4%) | 1,813 (30.5%) | 1,301 (33.4%) | NA | 2,171 (34.9%) | 548 (28.8%) | 802 (37%) |
| Number of persons who started the follow-up | 5,902 (94.3%) | 5,706 (95.9%) | 3,659 (93.8%) | NA | 5,863 (94.4%) | 1,759 (92.5%) | 2,067 (95.3%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 18,356 | 19,701 | 6,145 | NA | 18,398 | 3,385 | 6,180 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 0 | NA | 2 | 0 | 3 |
| Number of people with vaccinations (n/%): 0 | 1,424 (22.7%) | 4,383 (73.7%) | 1,964 (50.4%) | 0 (NA%) | 1,631 (26.3%) | 1,059 (55.7%) | 300 (13.8%) |
| Number of people with vaccinations (n/%): 1 | 605 (9.7%) | 560 (9.4%) | 681 (17.5%) | 0 (NA%) | 463 (7.5%) | 270 (14.2%) | 150 (6.9%) |
| Number of people with vaccinations (n/%): 2 | 750 (12%) | 286 (4.8%) | 588 (15.1%) | 0 (NA%) | 844 (13.6%) | 201 (10.6%) | 235 (10.8%) |
| Number of people with vaccinations (n/%): 3 or more | 3,123 (49.9%) | 477 (8%) | 426 (10.9%) | 0 (NA%) | 2,925 (47.1%) | 229 (12%) | 1,382 (63.7%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 47 describes comorbidities at baseline of SLE patients across databases. PEDIANET did not have patients for this cohort. Cancer diagnosis was identified in a range from 3.3% in BIFAP to 5.3% to 8.2% in NHR. SNDS reports the highest prevalence of drug use across most therapeutic groups, with some exceptions. Use of drugs to treat mental health diseases, lipid lowering drugs, cardiovascular medications, and anti-epileptics were comparable across data sources, with some few exceptions. CPRD shows the highest use of drugs to treat mental health disorders (34.7%) and the lowest use of

anti-epileptics (4.8%), while lower percentages of lipid lowering drugs use were found in SNDS (13.2%) as well as lower usage of cardiovascular medication in NHR (18.8%). Use of TNF inhibitor were slightly higher in SNDS (1.5%) and NHR (1.8%) compared to other databases (<1%). Of note, the recorded use of sex hormones in SNDS (21.6%) was five times higher than VID, BIFAP, SIDIAP and NHR, while CRPD recorded 18%. Prevalence of antibiotic use in SLE patients during look back was between 31.5 to 55.1% across databases.

*Table 47. Comorbidities in the study cohort with SLE.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,261 | 5,949 | 3,899 | 0 | 6,213 | 1,901 | 2,169 |
| Immunocompromise status (n/%) | 623 (10%) | 1,164 (19.6%) | 834 (21.4%) | 0 (0%) | 823 (13.2%) | 231 (12.2%) | 548 (25.3%) |
| Malignancy (n/%) | 204 (3.3%) | 208 (3.5%) | 169 (4.3%) | 0 (0%) | 234 (3.8%) | 124 (6.5%) | 178 (8.2%) |
| Celiac disease (n/%) | 6 (0.1%) | 16 (0.3%) | 5 (0.1%) | 0 (0%) | 7 (0.1%) | < 5 | 8 (0.4%) |
| Atopic dermatitis (n/%) | 219 (3.5%) | 118 (2%) | 24 (0.6%) | 0 (0%) | 425 (6.8%) | < 5 | 264 (12.2%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 1,557 (24.9%) | 2,198 (36.9%) | 1,293 (33.2%) | 0 (0%) | 1,752 (28.2%) | 876 (46.1%) | 673 (31%) |
| Immunostimulants (n/%) | 0 (0%) | < 5 | 8 (0.2%) | 0 (0%) | 0 (0%) | 9 (0.5%) | < 5 |
| Analgesics (n/%) | 2,675 (42.7%) | 2,380 (40%) | 2,070 (53.1%) | 0 (0%) | 3,067 (49.4%) | 1,477 (77.7%) | 832 (38.4%) |
| Systemic corticosteroids (n/%) | 1,399 (22.3%) | 1,796 (30.2%) | 1,087 (27.9%) | 0 (0%) | 1,605 (25.8%) | 831 (43.7%) | 587 (27.1%) |
| Antithrombotic agents (n/%) | 1,353 (21.6%) | 1,355 (22.8%) | 944 (24.2%) | 0 (0%) | 1,447 (23.3%) | 468 (24.6%) | 484 (22.3%) |
| Sex hormones (n/%) | 267 (4.3%) | 1,066 (17.9%) | 153 (3.9%) | 0 (0%) | 252 (4.1%) | 410 (21.6%) | 0 (0%) |
| Diabetes medications (n/%) | 472 (7.5%) | 386 (6.5%) | 280 (7.2%) | 0 (0%) | 461 (7.4%) | 100 (5.3%) | 111 (5.1%) |
| Antibiotics (n/%) | 1,973 (31.5%) | 2,675 (45%) | 1,693 (43.4%) | 0 (0%) | 2,161 (34.8%) | 1,047 (55.1%) | 829 (38.2%) |
| Antiviral drugs (n/%) | 95 (1.5%) | 201 (3.4%) | 97 (2.5%) | 0 (0%) | 107 (1.7%) | 119 (6.3%) | 57 (2.6%) |
| Antimycotics (n/%) | 97 (1.5%) | 180 (3%) | 0 (0%) | 0 (0%) | 80 (1.3%) | 97 (5.1%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 1,937 (30.9%) | 1,208 (20.3%) | 1,638 (42%) | 0 (0%) | 2,186 (35.2%) | 0 (0%) | 712 (32.8%) |
| Drug to treat mental health diseases (n/%) | 1,309 (20.9%) | 2,066 (34.7%) | 844 (21.6%) | 0 (0%) | 1,405 (22.6%) | 322 (16.9%) | 336 (15.5%) |
| Lipid lowering drugs (n/%) | 1,132 (18.1%) | 1,127 (18.9%) | 851 (21.8%) | 0 (0%) | 1,186 (19.1%) | 250 (13.2%) | 410 (18.9%) |
| Cardiovascular medication (n/%) | 2,495 (39.8%) | 2,635 (44.3%) | 1,815 (46.6%) | 0 (0%) | 2,686 (43.2%) | 740 (38.9%) | 407 (18.8%) |
| Oncologic drugs (n/%) | 83 (1.3%) | 151 (2.5%) | 81 (2.1%) | 0 (0%) | 80 (1.3%) | 76 (4%) | 24 (1.1%) |
| Anti-epileptics (n/%) | 576 (9.2%) | 284 (4.8%) | 406 (10.4%) | 0 (0%) | 628 (10.1%) | 168 (8.8%) | 147 (6.8%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 9 (0.2%) | 27 (0.7%) | 0 (0%) | 0 (0%) | 28 (1.5%) | 39 (1.8%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.3 IRs of SLE flares

#### 10.6.3.1 IRs of SLE flares in the general population

In BIFAP, 2,757 people developed a first SLE flare, with IRs of 319.3 per 1000 PY (CI95% 307.5-331.5). In CPRD, 2,246 individuals developed a first SLE flare, with IRs of 175.8 per 1,000 PY (CI95% 168.6-183.2). In VID, 1,352 people developed a first flare-up, leading to an IR of 354.6 per 1,000 PY (CI95% (335.9-374). In SIDIAP, 2,902 patients developed a first flare-up accounting for an IR of 343.4 per 1,000 PY (CI95% (331-356.1). In SNDS, 8655 subjects flared-up, leading to an IR of first flare-up episode of 518.8 per 1,000 PY (CI 95% 484.8-554.5). Finally, in NHR, 787 patients developed a first flare up, leading to an IR of 257.4 per 1000 PY (CI 95% 239.7-276).

A consequential decrease of the IRs is observed for the second and third flares in all data sources. IRs of second flares were lower in all data sources compared to the first flare incidence. IRs per 1,000 PY were 182.3 in BIFAP, 118.5 in CPRD, 172.9 in VID, 171.1 in SIDIAP, 292.9 in SNDS, and 167.4 NHR.

IRs of third flares episodes were lower in all data sources compared to the second flare incidence, except for 33% increment in NHR (IRs 222.9 per 1,000PY). Across the other data sources, the decline ranged from 7% to 30%. IRs per 1,000 PY were 128.2 in BIFAP, 104.8 in CPRD, 141.1 in VID, 128.3 in SIDIAP, and 272.3 in SNDS. See Table 48 below.

*Table 48. Background incidence rate of first, second, and third flare in the SLE cohort, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 6,261 | 5,949 | 3,899 | 0 | 6,213 | 1,901 | 2,169 |
| Number of persons who started the follow-up | 5,833 | 5,659 | 3,611 | NA | 5,831 | 1,710 | 2,048 |
| Number of persons who develop a first flare-up episode | 2,757 | 2,246 | 1,352 | NA | 2,902 | 865 | 787 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 319.3 (307.5-331.5) | 175.8 (168.6-183.2) | 354.6 (335.9-374) | NA | 343.4 (331-356.1) | 518.8 (484.8-554.5) | 257.4 (239.7-276) |
| Number of persons still in the study 90 days after first flare | 2,570 | 2,094 | 1,194 | NA | 2,822 | 789 | 740 |
| Number of persons who develop a second flare-up episode | 709 | 511 | 177 | NA | 741 | 239 | 168 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 182.3 (169.1-196.2) | 118.5 (108.5-129.2) | 172.9 (148.4-200.3) | NA | 171.1 (159-183.9) | 292.9 (257-332.5) | 167.4 (143-194.7) |
| Number of persons still in the study 90 days after second flare | 637 | 476 | 146 | NA | 718 | 204 | 152 |
| Number of persons who develop a third flare-up episode | 118 | 91 | 13 | NA | 129 | 45 | 37 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 128.2 (106.1-153.5) | 104.8 (84.3-128.6) | 141.1 (75.1-241.3) | NA | 128.3 (107.1-152.4) | 272.3 (198.6-364.4) | 222.9 (156.9-307.2) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.3.2 IRs of SLE flares stratified per age categories

Most of the people experiencing flares of SLE were adults ≥ 18 years old, followed by ≥ 60 years old and then 0-17 years old individuals. Overall, the incidence of flares decreased from the first episode to the second one for all the data sources and age categories, except for NHR 0-17-year-olds (first flare IR = 274.1 per 1000 PY; second flare IR = 1164.5 per 1000 PY). No cases were found in PEDIANET. Overall, rates for all episodes were slightly higher for 0-17 and 18-59 years old if compared to the≥60 age category. However, the highest IRs of 1164.5 (678.4-1864.5) are observed for NHR second flare episodes in 0–17-year-olds.

For the 0-17-year-old category, the IRs of the first flare ranged from 288.3 (BIFAP) to 671.8 (SNDS) per 1000 PY, the IRs of the second flare episodes span from 144 (CPRD) to 369.5 (VID) per 1000 PY. For the 18-59-year-old category, the IRs per 1000 PY of the first flare ranged from 196.5 (CPRD) to 569.1 (SNDS), the IRs of the second flare episodes span from 188.7 (SIDIAP) to 319.9 (SNDS). For the ≥ 60 years category, the IRs per 1000 PY of the first flare ranged from 133 (CPRD) to 401.1 (SNDS), and the IRs of the second flare episodes span from 82.7 (CPRD) to 210.9 (SNDS).

Regarding the third flare episodes, few (<5) or no cases were reported for the 0-17-year-old category. Higher third flares IRs for the 18-59 years category spanning from 116.1 (CPRD) to 306 (SNDS) per 1000 PY were found compared to the ≥60 years category, ranging from 63.9 (NHR) to 118.3 (SNDS) per 1000 PY. Third-flare IRs were higher than the second-episode values only in BIFAP, SIDIAP, and SNDS in 0-17-year-olds and NHR in 18-59-year-olds.

*Table 49. Background incidence rate of first, second, and third flare in the SLE cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 110 | 71 | 37 | NA | 44 | 27 | 33 |
| Number of persons who develop a first flare-up episode | 18-59 | 1,800 | 1,553 | 900 | NA | 1,967 | 628 | 518 |
| Number of persons who develop a first flare-up episode | 60+ | 847 | 622 | 415 | NA | 891 | 210 | 236 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 288.3 (237-347.5) | 365.3 (285.3-460.8) | 412.9 (290.7-569.2) | NA | 328.8 (238.9-441.3) | 671.8 (442.7-977.4) | 274.1 (188.7-385) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 354.1 (338-370.9) | 196.5 (186.8-206.5) | 371.7 (347.8-396.8) | NA | 380.9 (364.3-398.1) | 569.1 (525.4-615.4) | 294.8 (269.9-321.3) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 267.2 (249.5-285.8) | 133 (122.7-143.8) | 318.8 (288.9-351) | NA | 282.5 (264.3-301.7) | 401.1 (348.6-459.1) | 200 (175.3-227.2) |
| Number of persons still in the study 90 days after first flare | 0-17 | 102 | 62 | 29 | NA | 41 | 26 | 28 |
| Number of persons still in the study 90 days after first flare | 18-59 | 1,688 | 1,468 | 787 | NA | 1,927 | 579 | 487 |

| Characteristics | Age band | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons still in the study 90 days after first flare | 60+ | 902 | 677 | 399 | NA | 972 | 203 | 255 |
| Number of persons who develop a second flare-up episode | 0-17 | 19 | 11 | 8 | NA | 7 | 7 | 17 |
| Number of persons who develop a second flare-up episode | 18-59 | 499 | 386 | 117 | NA | 545 | 189 | 113 |
| Number of persons who develop a second flare-up episode | 60+ | 191 | 114 | 52 | NA | 189 | 43 | 38 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 147.6 (88.9-230.5) | 144 (71.9-257.6) | 369.5 (159.5-728.1) | NA | 148.3 (59.6-305.5) | 330.2 (132.8-680.4) | 1164.5 (678.4-1864.5) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 199.4 (182.3-217.7) | 135.1 (121.9-149.2) | 171.7 (142-205.8) | NA | 188.7 (173.2-205.2) | 319.9 (275.9-368.9) | 173.3 (142.8-208.3) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 151.8 (131.1-175) | 82.7 (68.3-99.4) | 162.1 (121-212.5) | NA | 135.4 (116.8-156.2) | 210.9 (152.7-284.1) | 112.8 (79.9-154.9) |
| Number of persons still in the study 90 days after second flare | 0-17 | 14 | 10 | 6 | | < 5 | 5 | 10 |
| Number of persons still in the study 90 days after second flare | 18-59 | 461 | 365 | 96 | | 526 | 160 | 106 |
| Number of persons still in the study 90 days after second flare | 60+ | 182 | 117 | 48 | | 213 | 41 | 40 |
| Number of persons who develop a third flare-up episode | 0-17 | < 5 | 0 | 0 | | < 5 | < 5 | NR |
| Number of persons who develop a third flare-up episode | 18-59 | 95 | 76 | 10 | | 101 | 39 | NR |
| Number of persons who develop a third flare-up episode | 60+ | 20 | 15 | < 5 | | 27 | < 5 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 154.9 (31.9-452.6) | 0 (0-354.9) | 0 (0-1138) | NA | 213.6 (5.4-1,190.1) | 502.4 (60.8-1,814.9) | 541.1 (175.7-1,262.8) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 144.5 (116.9-176.7) | 116.1 (91.5-145.3) | 165.5 (79.4-304.4) | NA | 139.6 (113.7-169.6) | 306 (217.6-418.3) | 264 (176.8-379.2) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 82.1 (50.1-126.8) | 73.6 (41.2-121.4) | 105.5 (21.7-308.2) | NA | 97.4 (64.2-141.7) | 118.3 (32.2-303) | 63.9 (13.2-186.8) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.3.3 IRs of SLE flares stratified per gender

Across data sources, the number of females who developed a first episode of SLE flares and their incidence was higher than that of males, as shown in Table 50. This is in line with the reported evidence about SLE being a disease that mainly affects females (49). The IRs per 1000 PY of first SLE flares for females ranged from 178.1 (CPRD) to 552.7 (SNDS) per 1000 PY, while male rates moved from 155.7 (CPRD) to 375.6 (SNDS) per 1000 PY. The number of cases and the IRs per 1000 PY of second SLE flares were lower

than the first episodes and still higher for females except in NHR and CPRD. Overall, the second SLE flares ranged from 118.4 (CPRD) to 298.2 (SNDS) per 1000 PY in females, while male rates moved from 119.8 (CPRD) to 257.4 (SNDS) per 1000 PY. The number of cases and the IRs per 1000 PY of third SLE flares were lower or comparable to values of the second episodes, except for males in SNDS and females in NHR, and still higher for females, except in SNDS. Overall, the third SLE flares ranged from 108.9 (CPRD) to 269 (SNDS) per 1000 PY in females, while male rates moved from 63.3 (CPRD) to 302.3 (SNDS) per 1000 PY.

*Table 50. Background incidence rate of first, second, and third flare in the SLE cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 2,219 | 2,038 | 1,138 | NA | 2,436 | 745 | 621 |
| Number of persons who develop a first flare-up episode | M | 538 | 208 | 214 | NA | 466 | 120 | 166 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 336.7 (322.9-351) | 178.1 (170.5-186) | 371.2 (349.9-393.4) | NA | 358.7 (344.6-373.2) | 552.7 (513.8-593.9) | 268.1 (247.4-290) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 263.2 (241.4-286.4) | 155.7 (135.3-178.4) | 286.6 (249.5-327.7) | NA | 280.8 (255.9-307.5) | 375.6 (311.4-449.1) | 223.9 (191.2-260.7) |
| Number of persons still in the study 90 days after first flare | F | 2,069 | 1,899 | 1,003 | NA | 2,372 | 679 | 590 |
| Number of persons still in the study 90 days after first flare | M | 501 | 195 | 191 | NA | 450 | 110 | 150 |
| Number of persons who develop a second flare-up episode | F | 592 | 467 | 153 | NA | 636 | 212 | 134 |
| Number of persons who develop a second flare-up episode | M | 117 | 44 | 24 | NA | 105 | 27 | 34 |
| IR of second flare-up episode, per 1,000 PY PY (CI 95%) | F | 186 (171.3-201.6) | 118.4 (107.9-129.6) | 180.4 (153-211.4) | NA | 173.7 (160.5-187.7) | 298.2 (259.4-341.1) | 162.5 (136.2-192.5) |
| IR of second flare-up episode, per 1,000 PY PY (CI 95%) | M | 165.9 (137.2-198.9) | 119.8 (87.1-160.8) | 136.5 (87.5-203.2) | NA | 156.9 (128.3-189.9) | 257.4 (169.6-374.5) | 189.8 (131.5-265.3) |
| Number of persons still in the study 90 days after second flare | F | 536 | 435 | 126 | | 619 | 179 | 120 |
| Number of persons still in the study 90 days after second flare | M | 101 | 41 | 20 | | 99 | 25 | 32 |
| Number of persons who develop a third flare-up episode | F | 100 | 86 | 11 | | 115 | 40 | 30 |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | M | 18 | 5 | < 5 | | 14 | 5 | 7 |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | F | 130.7 (106.3-158.9) | 108.9 (87.1-134.5) | 141.4 (70.6-253.1) | NA | 133.4 (110.1-160.1) | 269 (192.2-366.3) | 232.6 (157-332.1) |
| IR of third flare-up episode, per 1,000 PY PY (CI 95%) | M | 116.1 (68.8-183.4) | 63.3 (20.6-147.7) | 139.5 (16.9-503.9) | NA | 97.4 (53.3-163.5) | 302.3 (98.2-705.5) | 188.8 (75.9-389) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.3.4 IRs of SLE flares in pregnant population

VID identified 60 pregnant women who had at least one pregnancy after the start of follow-up for the SLE cohort population. The IR per 1,000 PY of the first flare episode of SLE among pregnant people in VID was 369.3 (CI 95% 159.4-727.7) with 8 observed events. SIDAP identified 54 pregnant women who had at least one pregnancy after the start of follow-up for the SLE cohort population. The IR per 1,000 PY of the first flare episode of SLE among pregnant population in SIDAP was 245.7 (CI 95% 90.2-534.8) with 6 observed events. NHR identified 86 pregnant women who had at least one pregnancy after the start of follow-up for the SLE cohort population. The IR per 1,000 PY of the first flare episode of SLE among pregnant population in NHR was 106.7 (CI 95%29.1-273.2) but with only <5 observed events. Across these 3 data sources, <5 pregnant women did also experience a second and third flare episode. CPRD, BIFAP, PEDIANET (adolescents up to 14 years of age) and SNDS did not run the pregnancy algorithm. See Table 51.

*Table 51 Background IR in pregnant population of first, second, and third flare in the SLE cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 60 | 54 | NA | 86 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 8 | 6 | NA | < 5 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 369.3 (159.4-727.7) | 245.7 (90.2-534.8) | NA | 106.7 (29.1-273.2) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | 17 | 26 | NA | 30 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | < 5 | NA | < 5 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 321.2 (38.9-1,160.4) | 302 (82.3-773.2) | NA | 79.9 (2-445.3) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | < 5 | 5 | NA | < 5 |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | 0 | 0 | NA | 0 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-9,488.5) | 0 (0-2,069.7) | NA | 0 (0-3,148) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.6.4 Six- and twelve-months cumulative incidence of flares of SLE

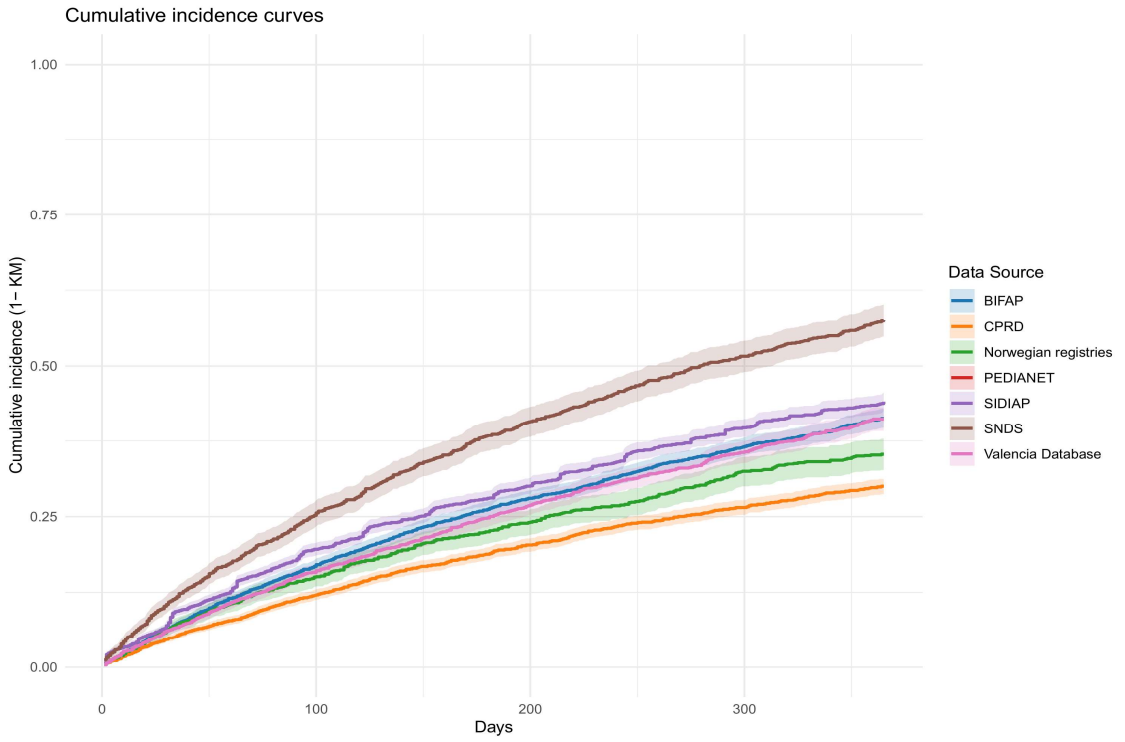
Table 52 shows the 6- and 12-months cumulative incidence of the first flare of SLE. The 6-month risk of a first flare in SLE patients was 24.8% for VID, 28% for SIDAP, 38.4% for SNDS, 22.5% for NHR, 26.2% for BIFAP, and 18.8% for CPRD. The 1-year risk of a flare was 41.2% in VID, 44.1% in SIDAP, 57.6% in SNDS, 35.3% in NHR, 41.3% in BIFAP and 30% in CPRD. The cumulative incidence curve is represented in Figure 14.

*Table 52 Six- and twelve-months cumulative incidence of flares of SLE (95% confidence interval)*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|
| 180 | 0.225 (0.205-0.245) | 0.248 (0.233-0.263) | 0.28 (0.268-0.293) | 0.262 (0.25-0.275) | 0.384 (0.359-0.408) | 0.188 (0.178-0.199) |
| 365 | 0.353 (0.327-0.379) | 0.412 (0.392-0.431) | 0.441 (0.425-0.456) | 0.413 (0.397-0.429) | 0.576 (0.549-0.601) | 0.3 (0.287-0.312) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 14 Cumulative incidence curse of SLE*

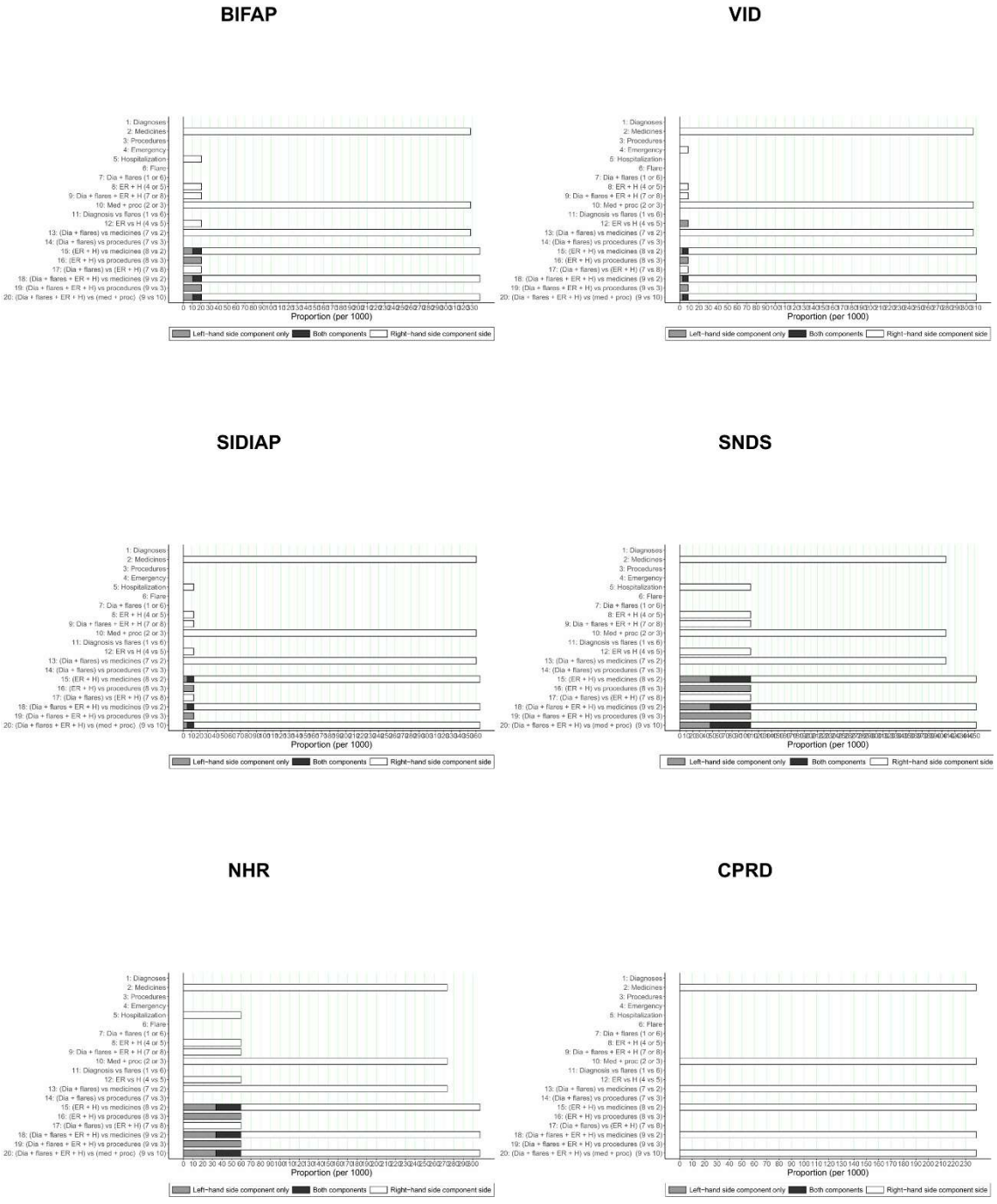



### 10.6.5 Other analyses

#### 10.6.5.1 Component analysis

MED was the highest component of the 12-month cumulative incidence of the first SLE flare episode in all data sources, ranging from 89% (NHR) to 100% (CPRD) (see Figure 15). The remaining cases were identified from H across data sources, except for VID, with ER. The overlapping of MED and H or ER components ranged from 1.8% (VID) to 13.7% (SNDS).

*Figure 15 Component Analysis of SLE*



## 10.7 RHEUMATOID ARTHRITIS (RA)

### 10.7.1 Attrition of the study population

In CPRD, 55,568 subjects entered the RA cohort followed by 40,406 in NHR, 22,039 in BIFAP, 17,444 in SIDIAP, 15,992 in VID and 11,884 in SNDS. From them, 53,697 persons entered the follow-up in CPRD, 38,592 in NHR, 20,589 in BIFAP, 16,158 in SIDIAP, 14,921 in VID and 10,689 in SNDS. Finally, In the Italian PEDIANET database (paediatric population), there were only 6 RA cases identified, all of them started the follow-up. See Table 53 below.

*Table 53 Characteristics of the study RA cohort*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 36,962 | 93,126 | 32,653 | 9 | 21,979 | 21,072 | 95,527 |
| Disease codes found during lookback | 14923 | 37558 | 16661 | < 5 | 4535 | 9188 | 55121 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Rheumatoid arthritis | 22,039 | 55,568 | 15,992 | 6 | 17,444 | 11,884 | 40,406 |
| Persons dying before entrance in the follow-up | 471 | 301 | 203 | 0 | 502 | 264 | 142 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 979 | 1,570 | 868 | 0 | 784 | 931 | 1,672 |
| Persons entering follow-up | 20,589 | 53,697 | 14,921 | 6 | 16,158 | 10,689 | 38,592 |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.7.2 Characteristics of the study cohort

The total RA study cohort that started follow up across databases comprised 154,652 individuals. The total follow-up time ranged between 20,193 PY in SNDS to 181,120 PY in CPRD, while in PEDIANET was 16 PY. Across data sources, between 60.4% to 71% of the cohort population were females. The median age was between 57- to 66-year-old across data sources, except for PEDIANET (4.5 years old). These data are aligned with previous demographic knowledge about RA in the general population (50–52).
The percentage of people with at least 3 vaccinations during follow-up was from 9.5% in CPRD to 65.3% in NHR. See Table 54.

*Table 54 Characteristics of the study RA cohort*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 22,039 | 55,568 | 15,992 | 6 | 17,444 | 11,884 | 40,406 |
| Female (n/%) | 15,171 (68.8%) | 38,404 (69.1%) | 11,138 (69.6%) | < 5 | 12,361 (70.9%) | 7,987 (67.2%) | 24,386 (60.4%) |
| Male (n/%) | 6,868 (31.2%) | 17,164 (30.9%) | 4,854 (30.4%) | < 5 | 5,083 (29.1%) | 3,897 (32.8%) | 16,020 (39.6%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 51 | 53 | 51 | 2 | 53 | 53 | 42 |
| Age in year (IQR): PCT 50 | 62.0 | 64.0 | 62.0 | 4.5 | 65.0 | 66.0 | 57.0 |
| Age in year (IQR): PCT 75 | 75 | 74 | 73 | 10 | 76 | 77 | 70 |
| Age in categories (n/%): < 18 | 407 (1.8%) | 157 (0.3%) | 221 (1.4%) | 6 (100%) | 100 (0.6%) | 61 (0.5%) | 1,258 (3.1%) |
| Age in categories (n/%): 18-59 | 9,306 (42.2%) | 22,025 (39.6%) | 6,968 (43.6%) | 0 (0%) | 6,718 (38.5%) | 4,375 (36.8%) | 21,046 (52.1%) |
| Age in categories (n/%): > 60 | 12,326 (55.9%) | 33,386 (60.1%) | 8,803 (55%) | 0 (0%) | 10,626 (60.9%) | 7,448 (62.7%) | 18,102 (44.8%) |
| Number of persons who started the follow-up | 20,589 (93.4%) | 53,697 (96.6%) | 14,921 (93.3%) | 6 (100%) | 16,158 (92.6%) | 10,689 (89.9%) | 38,592 (95.5%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 62,705 | 181,120 | 24,673 | 16 | 49,522 | 20,193 | 114,761 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 1 | 1 | 3 | 1 | 4 |
| Number of people with vaccinations (n/%): 0 | 4,341 (19.7%) | 40,218 (72.4%) | 6,648 (41.6%) | < 5 | 3,862 (22.1%) | 4,412 (37.1%) | 5,096 (12.6%) |
| Number of people with vaccinations (n/%): 1 | 2,062 (9.4%) | 5,206 (9.4%) | 3,190 (19.9%) | 0 (0%) | 1,297 (7.4%) | 2,167 (18.2%) | 2,956 (7.3%) |
| Number of people with vaccinations (n/%): 2 | 2,523 (11.4%) | 2,994 (5.4%) | 2,907 (18.2%) | < 5 | 2,069 (11.9%) | 1,646 (13.9%) | 4,153 (10.3%) |
| Number of people with vaccinations (n/%): 3 or more | 11,663 (52.9%) | 5,279 (9.5%) | 2,176 (13.6%) | < 5 | 8,930 (51.2%) | 2,464 (20.7%) | 26,387 (65.3%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 55 describes comorbidities at baseline of RA patients in all databases. Cancer diagnosis was identified in a range from 3.4% in BIFAP to 11% in SNDS. No Malignancies were observed in PEDIANET. Infections accounted for 35% to 56.4% across data sources, except for PEDIANET (<5 cases). SNDS reports the highest prevalence of drug use across most therapeutic groups, with some exceptions. Diabetes medications were slightly higher in VID and SIDIAP. Drugs to treat mental health disease were higher in CPRD (29.8%) and lower in SNDS (14.3%), lipid lowering drugs were higher in CPRD (32.8%) and lower in NHR (22%), and anti-epileptics were also higher

in NHR (13.1%) and lower in CPRD (2.2%). No NSAIDs were found in SNDS, whereas accounted from 35% (CPRD) to 52.6% (VID) in the rest of databases except for PEDIANET. TNF inhibitor values were higher in SNDS (2.9%), VID (6%) and NHR (4.9%) than the other data sources (≤1%).

*Table 55 Comorbidities in the study cohort with RA.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 22,039 | 55,568 | 15,992 | 6 | 17,444 | 11,884 | 40,406 |
| Immunocompromise status (n/%) | 4279 (19.4%) | 17922 (32.3%) | 7616 (47.6%) | < 5 | 5,013 (28.7%) | 2,982 (25.1%) | 13,581 (33.6%) |
| Malignancy (n/%) | 756 (3.4%) | 2,292 (4.1%) | 1,144 (7.2%) | 0 (0%) | 877 (5%) | 1,311 (11%) | 2,600 (6.4%) |
| Cardiocerebrovascular disease (n/%) | 10,011 (45.4%) | 29,630 (53.3%) | 8,737 (54.6%) | 0 (0%) | 9,373 (53.7%) | 6,651 (56%) | 9,193 (22.8%) |
| Infection (n/%) | 7,709 (35%) | 22,887 (41.2%) | 7,194 (45%) | < 5 | 6785 (38.9%) | 6,708 (56.4%) | 14,114 (34.9%) |
| Alcohol abuse (n/%) | 131 (0.6%) | 28 (0.1%) | 133 (0.8%) | 0 (0%) | 115 (0.7%) | 123 (1%) | 270 (0.7%) |
| Obesity (n/%) | 359 (1.6%) | 199 (0.4%) | 478 (3%) | 0 (0%) | 611 (3.5%) | 387 (3.3%) | 1,112 (2.8%) |
| Immunostimulants (n/%) | 0 (0%) | < 5 | 16 (0.1%) | 0 (0%) | 0 (0%) | 50 (0.4%) | 64 (0.2%) |
| Analgesics (n/%) | 10,972 (49.8%) | 28,483 (51.3%) | 10,228 (64%) | < 5 | 10,390 (59.6%) | 10,327 (86.9%) | 17,797 (44%) |
| Systemic corticosteroids (n/%) | 6,315 (28.7%) | 14,785 (26.6%) | 5,534 (34.6%) | < 5 | 7,129 (40.9%) | 7,462 (62.8%) | 13,533 (33.5%) |
| Antithrombotic agents (n/%) | 4,121 (18.7%) | 11,284 (20.3%) | 3,537 (22.1%) | 0 (0%) | 3,852 (22.1%) | 3,520 (29.6%) | 8,880 (22%) |
| Sex hormones (n/%) | 521 (2.4%) | 5,551 (10%) | 420 (2.6%) | 0 (0%) | 373 (2.1%) | 1,339 (11.3%) | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 7,750 (35.2%) | 26,648 (48%) | 8,358 (52.3%) | < 5 | 8,693 (49.8%) | 8,116 (68.3%) | 17,266 (42.7%) |
| Diabetes medications (n/%) | 2,445 (11.1%) | 5,950 (10.7%) | 2,203 (13.8%) | 0 (0%) | 2,315 (13.3%) | 1,355 (11.4%) | 3,063 (7.6%) |
| Antibiotics (n/%) | 6,472 (29.4%) | 22,018 (39.6%) | 6,802 (42.5%) | < 5 | 6,115 (35.1%) | 6,387 (53.7%) | 12,413 (30.7%) |
| Antiviral drugs (n/%) | 323 (1.5%) | 918 (1.7%) | 335 (2.1%) | 0 (0%) | 217 (1.2%) | 518 (4.4%) | 693 (1.7%) |
| Antimycotics (n/%) | 218 (1%) | 846 (1.5%) | 0 (0%) | 0 (0%) | 181 (1%) | 514 (4.3%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 8,414 (38.2%) | 19,410 (34.9%) | 8,413 (52.6%) | < 5 | 7,717 (44.2%) | 0 (0%) | 20,653 (51.1%) |
| Drug to treat mental health diseases (n/%) | 4,298 (19.5%) | 16,569 (29.8%) | 3,866 (24.2%) | 0 (0%) | 4,241 (24.3%) | 2,414 (20.3%) | 5,772 (14.3%) |
| Lipid lowering drugs (n/%) | 5,271 (23.9%) | 18,208 (32.8%) | 4,954 (31%) | 0 (0%) | 4,485 (25.7%) | 2,843 (23.9%) | 8,884 (22%) |
| Cardiovascular medication (n/%) | 9,814 (44.5%) | 29,458 (53%) | 8,685 (54.3%) | 0 (0%) | 9,295 (53.3%) | 6,596 (55.5%) | 8,274 (20.5%) |
| Oncologic drugs (n/%) | 300 (1.4%) | 1,505 (2.7%) | 653 (4.1%) | 0 (0%) | 344 (2%) | 976 (8.2%) | 471 (1.2%) |
| Anti-epileptics (n/%) | 1,906 (8.6%) | 1,215 (2.2%) | 2,090 (13.1%) | 0 (0%) | 2,028 (11.6%) | 1,172 (9.9%) | 2,198 (5.4%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 560 (1%) | 962 (6%) | 0 (0%) | 0 (0%) | 343 (2.9%) | 1,975 (4.9%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.7.3 IRs of RA flares

#### 10.7.3.1 IRs of RA flares in the general population

The number of individuals who developed a first RA flare episode in BIFAP was 9,106, leading to an IR of 315.4 (CI 95% 308.9-321.9). In CPRD the population with first flare was 23,942, leading to an IR of 225.9 per 1000 PY (CI 95% 223-228.7). In VID, 5,283 persons developed a first flare-up episode, leading to an IR of 359.6/1000 PY (CI 350-369.5). In SIDIAP, 7,231 patients developed a first flare-up episode accounting for an IR of 312.7/1,000 PY (CI95% 305.5-320). In SNDS, 4,418 subjects flared up, leading to an IR of first flare-up episode of 425.7 per 1,000 PY (CI 95% 413.3-438.5). Finally, in NHR, 14,415 patients developed a first flare, leading to an IR of 259.8 per 1000 PY (CI 95% 255.6-264.1).

Overall, the IRs of the second flare-up episodes decreased in all data sources, with observed 170.3 cases in BIFAP, 148.7 cases in CPRD, 183.4 in VID, 165 in SIDIAP, 261.3 in SNDS, and 148.2 in NHR per 1000 PY. On average, IRs of the second flare episode decreased by around 40% in relation to the first flare episode. Overall, the IRs of the third flare-up episode slightly decreased compared to the second flare episodes IRs in all data sources, but with a much lower magnitude compared to the decrease between first and second flare. The observed IRs for the third episode are 120.9 in BIFAP, 139 in CPRD, 175.2 in VID, 111.6 in SIDIAP, 242.5 in SNDS, and 175.6 in NHR per 1,000 PY. See Table 56 below. In summary, a consequential decrease of the IRs is observed for the second and third flares in all data sources, except the third flare rates in NHR which were higher than the second.

*Table 56. Background incidence rate of first, second, and third flare in the RA cohort, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 22,039 | 55,568 | 15,992 | 6 | 17,444 | 11,884 | 40,406 |
| Number of persons who started the follow-up | 20,349 | 53,263 | 14,674 | 6 | 16,033 | 10,427 | 38,231 |
| Number of persons who develop a first flare-up episode | 9,106 | 23,942 | 5,283 | < 5 | 7,231 | 4,418 | 14,415 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 315.4 (308.9-321.9) | 225.9 (223-228.7) | 359.6 (350-369.5) | 313.7 (38-1133) | 312.7 (305.5-320) | 425.7 (413.3-438.5) | 259.8 (255.6-264.1) |
| Number of persons still in the study 90 days after first flare | 8,409 | 22,489 | 4,679 | < 5 | 6,877 | 3,910 | 13,460 |
| Number of persons who develop a second flare-up episode | 2,188 | 6,596 | 709 | 0 | 1,718 | 1,014 | 2,895 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 170.3 (163.3-177.6) | 148.7 (145.1-152.3) | 183.4 (170.2-197.4) | 0 (0-481.7) | 165 (157.3-173) | 261.3 (245.5-277.9) | 148.2 (142.9-153.7) |
| Number of persons still in the study 90 days after second flare | 1,972 | 6,081 | 576 | NA | 1,622 | 860 | 2,605 |
| Number of persons who develop a third flare-up episode | 339 | 1,425 | 62 | NA | 255 | 178 | 546 |

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 120.9 (108.4-134.5) | 139 (131.9-146.4) | 175.2 (134.3-224.6) | NA | 111.6 (98.3-126.1) | 242.5 (208.2-280.9) | 175.6 (161.2-191) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.7.3.2 IRs of RA flares stratified per age categories

Most of the people experiencing 1 to 3 episodes of RA flares were adults, with comparable numbers between 18-59 years old and ≥ 60 years old. Lower numbers were registered for 0-17 years old individuals. Overall, the incidence of flares decreased from the first episode to the second one for all the data sources and age categories. Low than <5 or no cases were found in PEDIANET. Across all data sources, the highest IR of RA flares was found for 18- to 59-year-olds compared to the other age categories. The only exception is CPRD, with higher rates in individuals aged 0- 17. For the 0-17-year-old category, the IRs of the first flare ranged from 285.4 (BIFAP) to 353.2 (CPRD) per 1000 PY, and the IRs of the second flare episodes span from 84.4 (BIFAP) to 320.5 (CPRD) per 1000 PY. For the 18-59-year-old category, the IRs per 1000 PY of the first flare ranged from 295.7 (CPRD) to 587.4 (SNDS), while the IRs of the second flare episodes span from 166.4 (NHR) to 319.6 (SNDS). For the ≥ 60 years category, the IRs per 1000 PY of the first flare ranged from 192.1 (CPRD) to 346.8 (SNDS), while the IRs of the second flare episodes span from 121.5 (NHR) to 214.6 (SNDS). Regarding the third flare episodes, few (<5) or no cases were reported for the 0-17-year-old category, except in NHR (15 cases, IR = 178 per 1000 PY). Slightly higher or almost comparable third flares IRs for the 18-59 years category spanning from 111.4 (SIDIAP) to 246.8 (SNDS) per 1000 PY were found compared to the ≥60 years category, which ranged from 106.1 (VID) to 236.6 (SNDS) per 1000 PY. Third-flare IRs were higher than the second-episode values for 0-17-year-olds in CPRD, SNDS and NHR, for 18-59-year-olds in VID and NHR, and for the ≥60 years category in SNDS and NHR.

*Table 57. Background incidence rate of first, second, and third flare in the RA cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 177 | 54 | 64 | < 5 | 44 | 19 | 405 |
| Number of persons who develop a first flare-up episode | 18-59 | 4,246 | 10,143 | 2,563 | | 3,153 | 2,007 | 8,358 |
| Number of persons who develop a first flare-up episode | 60+ | 4,683 | 13,745 | 2,656 | | 4,034 | 2,392 | 5,652 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 285.4 (244.9-330.7) | 353.2 (265.3-460.9) | 330.7 (254.7-422.3) | 313.7 (38-1133) | 318.3 (231.3-427.3) | 299 (180-466.9) | 247.5 (223.9-272.8) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 369 (358-380.3) | 295.7 (289.9-301.5) | 418.2 (402.2-434.7) | NA | 377.8 (364.7-391.2) | 587.4 (562-613.7) | 300.9 (294.5-307.4) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 279.6 (271.6-287.7) | 192.1 (188.9-195.3) | 317.4 (305.5-329.7) | NA | 275.5 (267-284.1) | 346.8 (333-361) | 216.9 (211.3-222.6) |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons still in the study 90 days after first flare | 0-17 | 163 | 47 | 58 | < 5 | 39 | 17 | 372 |
| Number of persons still in the study 90 days after first flare | 18-59 | 3,945 | 9,508 | 2,243 | | 3,051 | 1,761 | 7,838 |
| Number of persons still in the study 90 days after first flare | 60+ | 4,708 | 14,032 | 2,513 | | 4,102 | 2,250 | 5,863 |
| Number of persons who develop a second flare-up episode | 0-17 | 19 | 16 | 9 | 0 | 7 | 5 | 82 |
| Number of persons who develop a second flare-up episode | 18-59 | 1,144 | 3,118 | 400 | NA | 849 | 550 | 1,863 |
| Number of persons who develop a second flare-up episode | 60+ | 1,025 | 3,462 | 300 | NA | 862 | 459 | 950 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 84.4 (50.8-131.8) | 320.5 (183.2-520.4) | 183.3 (83.8-347.9) | 0 (0-481.7) | 187.6 (75.4-386.4) | 238.7 (77.5-557) | 157.6 (125.4-195.7) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 194.7 (183.6-206.3) | 185.6 (179.2-192.2) | 212.9 (192.6-234.9) | NA | 195.9 (182.9-209.5) | 319.6 (293.5-347.5) | 166.4 (159-174.2) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 151.9 (142.8-161.5) | 125.8 (121.7-130.1) | 154.8 (137.8-173.3) | NA | 142.7 (133.3-152.5) | 214.6 (195.4-235.2) | 121.5 (113.9-129.5) |
| Number of persons still in the study 90 days after second flare | 0-17 | 16 | 15 | 8 | NA | 6 | 5 | 70 |
| Number of persons still in the study 90 days after second flare | 18-59 | 1,033 | 2,878 | 321 | NA | 815 | 474 | 1,687 |
| Number of persons still in the study 90 days after second flare | 60+ | 1,042 | 3,461 | 258 | NA | 891 | 403 | 983 |
| Number of persons who develop a third flare-up episode | 0-17 | 0 | < 5 | 0 | | < 5 | < 5 | 15 |
| Number of persons who develop a third flare-up episode | 18-59 | 200 | 759 | 47 | | 124 | 102 | 365 |
| Number of persons who develop a third flare-up episode | 60+ | 139 | 662 | 15 | | 130 | 75 | 166 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 0 (0-317) | 327.8 (89.3-839.3) | 0 (0-792.1) | NA | 79.4 (2-442.1) | 278.2 (7-1549.9) | 178 (99.6-293.5) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 132.8 (115.1-152.6) | 170.9 (158.9-183.5) | 226.1 (166.1-300.7) | NA | 111.4 (92.7-132.9) | 246.8 (201.2-299.5) | 186.2 (167.6-206.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 108.1 (90.9-127.6) | 114.2 (105.6-123.2) | 106.1 (59.4-175) | NA | 112 (93.6-133) | 236.6 (186.1-296.6) | 156 (133.1-181.6) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.7.3.3 IRs of RA flares stratified per gender

Across data sources, the number of females who developed a first or second episode of RA flares and their incidence was higher than that of males, as shown in Table 58. This is in line with the reported evidence about RA being a disease that mainly affects females (53). The IRs per 1000 PY of first RA flares for females ranged from 231.7 (CPRD) to 450.1 (SNDS), while male rates moved from 212.9 (CPRD) to 376.9 (SNDS). The number of cases and the IRs per 1000 PY of second RA flares were much lower than in the first episodes. Overall, the second RA flares ranged from 150.3 (NHR) to 272.3 (SNDS) per 1000 PY in females, while male rates moved from 134.8 (CPRD) to 234.5 (SNDS) per 1000 PY. The number of cases and the IRs per 1000 PY of third RA flares were lower or comparable to values of the second episodes, except for females in NHR and males in VID, SNDS, and NHR. Overall, the third RA flares ranged from 113.6 (SIDIAP) to 229.4 (SNDS) per 1000 PY in females, while male rates moved from 106 (SIDIAP) to 284.1 (SNDS) per 1000 PY.

*Table 58. Background incidence rate of first, second, and third flare in the RA cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 6582 | 16905 | 3752 | < 5 | 5240 | 3117 | 9073 |
| Number of persons who develop a first flare-up episode | M | 2524 | 7037 | 1531 | 0 | 1991 | 1301 | 5342 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 333.7 (325.7-341.9) | 231.7 (228.3-235.3) | 364.6 (353-376.5) | 362.7 (43.9-1310.2) | 323.3 (314.6-332.1) | 450.1 (434.4-466.1) | 278.2 (272.5-284) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 275.7 (265.1-286.7) | 212.9 (207.9-217.9) | 348 (330.8-365.9) | 0 (0-4277.3) | 287.8 (275.3-300.8) | 376.9 (356.7-397.9) | 233.6 (227.4-240) |
| Number of persons still in the study 90 days after first flare | F | 6088 | 15948 | 3328 | < 5 | 4999 | 2763 | 8470 |
| Number of persons still in the study 90 days after first flare | M | 2321 | 6541 | 1351 | | 1878 | 1147 | 4990 |
| Number of persons who develop a second flare-up episode | F | 1,637 | 4,859 | 527 | 0 | 1,257 | 749 | 1,848 |
| Number of persons who develop a second flare-up episode | M | 551 | 1,737 | 182 | NA | 461 | 265 | 1,047 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 175.2 (166.9-183.9) | 154.4 (150.1-158.8) | 189.9 (174.1-206.9) | 0 (0-481.7) | 166.5 (157.4-176) | 272.3 (253.1-292.5) | 150.3 (143.5-157.3) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 157.2 (144.3-170.9) | 134.8 (128.5-141.3) | 166.8 (143.4-192.8) | NA | 160.9 (146.6-176.3) | 234.5 (207.1-264.5) | 144.7 (136.1-153.7) |
| Number of persons still in the study 90 days after second flare | F | 1,473 | 4,508 | 430 | NA | 1,188 | 640 | 1,673 |
| Number of persons still in the study 90 days after second flare | M | 499 | 1,573 | 146 | NA | 434 | 220 | 932 |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | F | 248 | 1063 | 46 | | 190 | 128 | 368 |
| Number of persons who develop a third flare-up episode | M | 91 | 362 | 16 | | 65 | 50 | 178 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 116.3 (102.3-131.7) | 141.5 (133.1-150.2) | 173.2 (126.8-231) | NA | 113.6 (98-130.9) | 229.4 (191.4-272.8) | 186.6 (168-206.7) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 135.6 (109.2-166.5) | 132.2 (118.9-146.5) | 181.2 (103.6-294.3) | NA | 106 (81.8-135.1) | 284.1 (210.9-374.6) | 156.5 (134.4-181.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.7.3.4 IRs of RA flares in pregnant population

VID identified 89 pregnant women who have at least one pregnancy after the start of follow-up for the RA cohort population. The IR per 1,000 PY of the first flare episode of RA among pregnant population in VID was 348.8 (CI 95% 180.2-609.3) with 12 observed events. SIDAP identified 176 pregnant women who have at least one pregnancy after the start of follow-up for the RA cohort population. The IR per 1,000 PY of the first flare episode of RA among pregnant population in SIDAP was 333.8 (CI 95% 213.9-496.7) with 24 observed events. NHR identified 777 pregnant women who have at least one pregnancy after the start of follow-up for the RA cohort population. The IR per 1,000 PY of the first flare episode of RA among pregnant population in NHR was 138.5 (CI 95% 102.2-183.7) with 48 observed events. Across these 3 data sources, the episodes of second flares did drop consistently, with 6 cases in SIDIAP (IR: 228.5; CI 95% 83.9-497.4) and 18 in NHR (IR: 145.3; CI 95% 86.1-299.6), and <5 cases in VID. Across these 3 data sources, <5 or no pregnant women did experience a third flare episode. BIFAP, CPRD, PEDIANET (adolescents up to 14 years of age) and SNDS did not run the pregnancy algorithm. See Table 59 below.

*Table 59. IR in pregnant population of first, second, and third flare in the RA cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 89 | 176 | NA | 777 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 12 | 24 | NA | 48 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 348.8 (180.2-609.3) | 333.8 (213.9-496.7) | NA | 138.5 (102.2-183.7) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | 15 | 60 | NA | 289 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | 6 | NA | 18 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 684 (141.1-1998.9) | 228.5 (83.9-497.4) | NA | 145.3 (86.1-229.6) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | 6 | 13 | NA | 57 |

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | 0 | < 5 | NA | < 5 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-1111.7) | 360.7 (43.7-1303.1) | NA | 136.3 (28.1-398.4) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.7.4 Six- and twelve-months cumulative incidence of flares of RA

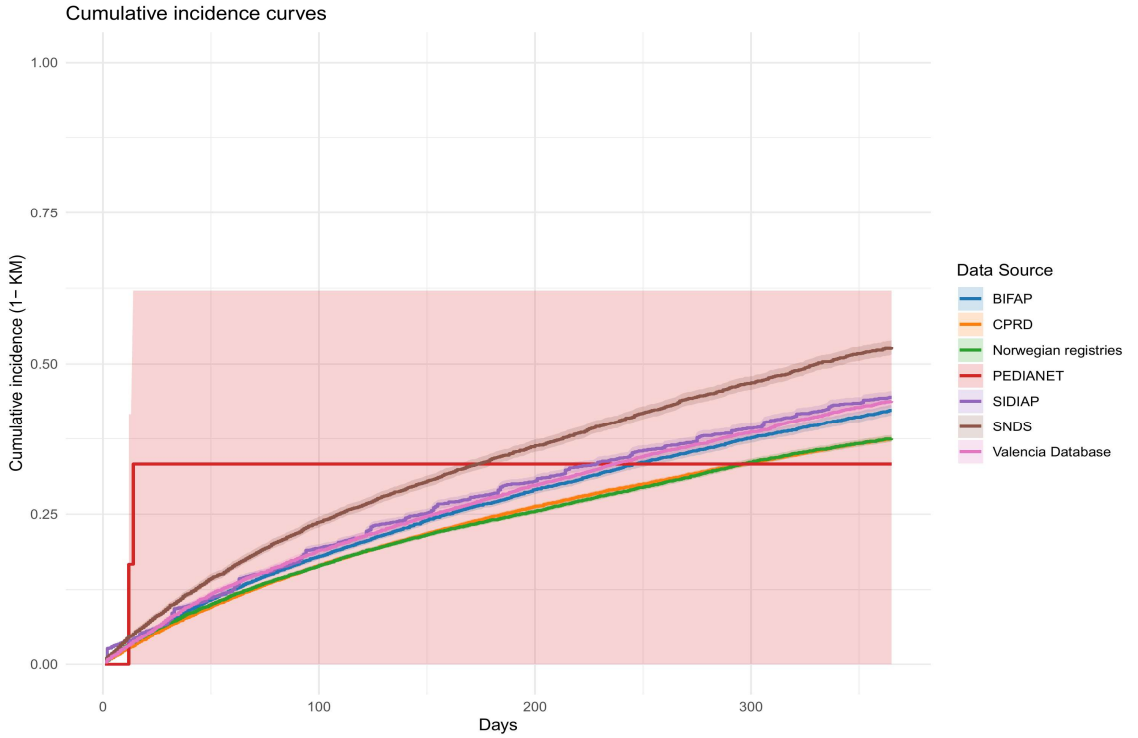
Table 60 shows the 6- and 12-months cumulative incidence of the first flare episode of RA. The 6-month risk of a first flare in RA patients was 27.8% for VID, 28.4% for SIDAP, 26.9% in BIFAP, 33.3% for PEDIANET, 34.2% for SNDS, 24.1% for NHR, and 24.6% for CPRD. The 12-month risk for RA patients of incurring a flare episode was 43.9% for VID, 44.5% for SIDAP, 33.3% in PEDIANET, 52.8% for SNDS, 37.6% for NHR, and 37.5% for CPRD. The cumulative incidence curve is represented in Figure 16.

*Table 60 Six- and twelve-months cumulative incidence of flares of RA (95% confidence interval)*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | PEDIANET-IT | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|---|
| 180 | 0.241 (0.236-0.245) | 0.278 (0.27-0.286) | 0.284 (0.276-0.292) | 0.269 (0.262-0.276) | 0.333 (0-0.621) | 0.342 (0.332-0.351) | 0.246 (0.242-0.25) |
| 365 | 0.376 (0.37-0.382) | 0.439 (0.429-0.449) | 0.445 (0.435-0.455) | 0.423 (0.414-0.432) | 0.333 (0-0.621) | 0.528 (0.516-0.539) | 0.375 (0.371-0.38) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 16. Cumulative incidence curve of RA.*

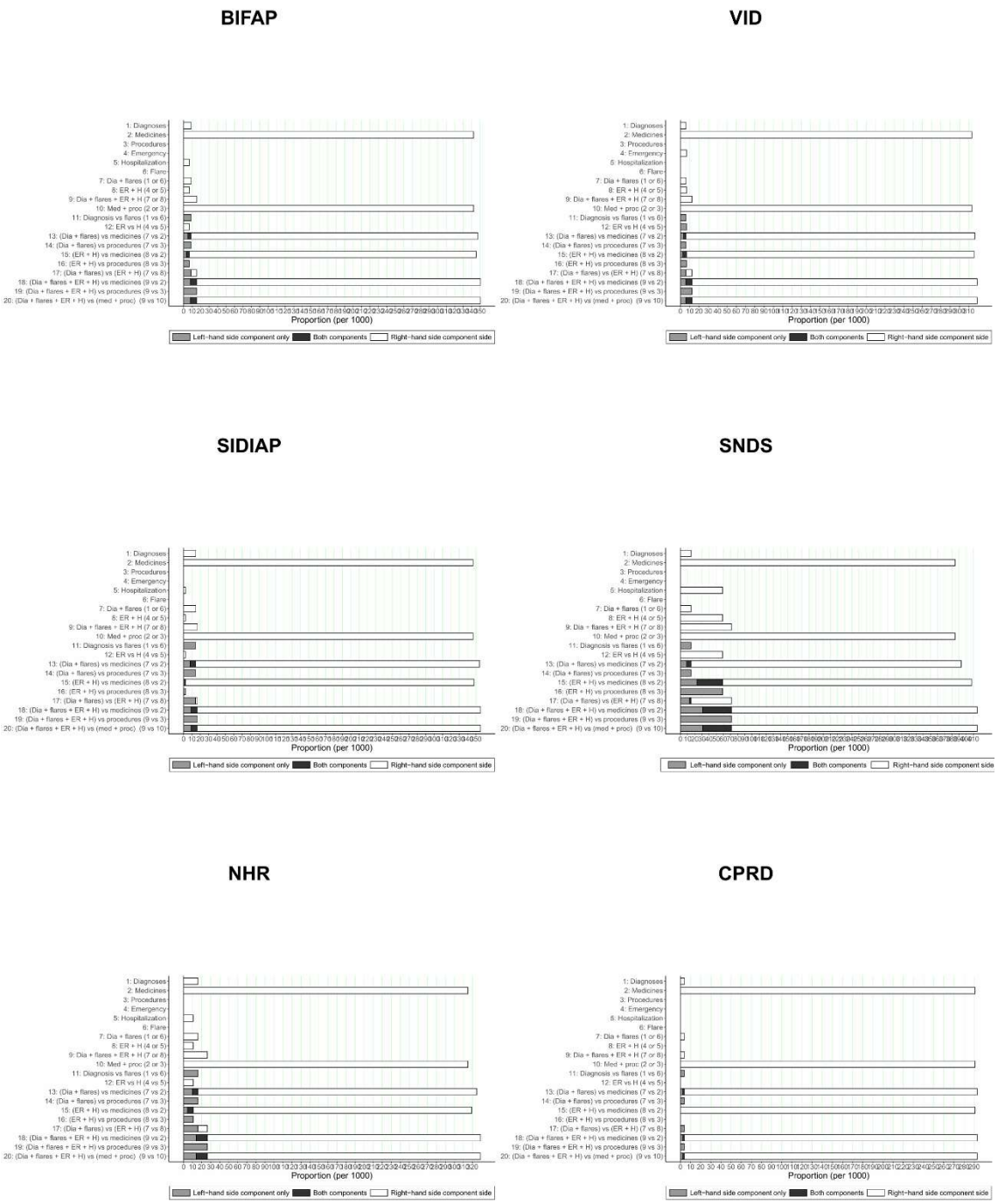


### 10.7.5 Other analyses

#### 10.7.5.1 Component analysis

MED was the highest component of the 12-month cumulative incidence of the first RA flare episode in all data sources, ranging from 92.5% in SNDS to 99.2% in CPRD (see Figure 17). The remaining cases were identified from DIA, H, and ER. The overlapping of MED and DIA or H or ER components ranged only from 0.6% (CPRD) to 9.7% (SNDS).

*Figure 17. Component Analysis for RA.*



## 10.8 PSORIATIC ARTHRITIS (PSA)

### 10.8.1 Attrition of the study population

After application of the exclusion criteria a total of 46,841 patients entered the PSA incident cohort, only in PEDIANET no cases were identified. More than 90% of the persons included in the study cohort started the follow-up across databases. The total number of persons who started the follow-up went from 1,276 in SNDS to 20,324 in CPRD. See Table 61 below.

*Table 61. Attrition table for the cohort with PSA*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birth date absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 5,680 | 30,183 | 7,769 | 0 | 7,611 | 1,820 | 23,667 |
| Disease codes found during lookback | 2,332 | 9,113 | 3,477 | 0 | 1,231 | 407 | 13,329 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Psoriatic arthritis | 3,348 | 21,070 | 4,292 | NA | 6,380 | 1,413 | 10,338 |
| Persons dying before entrance in the follow-up | 76 | 40 | 40 | 0 | 88 | 18 | 5 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 187 | 706 | 295 | 0 | 304 | 119 | 476 |
| Persons entering follow-up | 3,085 | 20,324 | 3,957 | NA | 5,988 | 1,276 | 9,857 |

### 10.8.2 Characteristics of the study cohort

Most of the PSA patients included in the study cohort were women (from 50.6% in BIFAP to 55.3% in SNDS), except in SIDIAP (49.7%). Median age of the total study population was between 52 and 59-years-old. Total follow-up time was from 2,508 PY in SNDS to 69,637 in CPRD.

Seventy-five percent of CPRD cohort population did not receive any vaccination after the cohort entry. It dropped to 44.1% in VID, 22.5% in SIDIAP, 36.9% in SNDS, 18.1 % in

BIFAP and 12.4% in NHR. In BIFAP, SIDIAP and NHR, more than 50% of the cohort population received 3 or more vaccines along the study period. See Table 62.

*Table 62. Characteristics of the PSA study cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 3,348 | 21,070 | 4,292 | 0 | 6,380 | 1,413 | 10,338 |
| Female (n/%) | 1,695 (50.6%) | 11,121 (52.8%) | 2,297 (53.5%) | 0 (NA%) | 3,174 (49.7%) | 782 (55.3%) | 5,706 (55.2%) |
| Male (n/%) | 1,653 (49.4%) | 9,949 (47.2%) | 1,995 (46.5%) | 0 (NA%) | 3,206 (50.3%) | 631 (44.7%) | 4,632 (44.8%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 50 | 41 | 46 | NA | 47 | 46 | 41 |
| Age in year (IQR): PCT 50 | 59 | 52 | 55 | NA | 57 | 56 | 52 |
| Age in year (IQR): PCT 75 | 69 | 62 | 64 | NA | 67 | 68 | 62 |
| Age in categories (n/%): < 18 | 14 (0.4%) | 118 (0.6%) | 31 (0.7%) | 0 (NA%) | 22 (0.3%) | 8 (0.6%) | 99 (1%) |
| Age in categories (n/%): 18-59 | 1,701 (50.8%) | 14,469 (68.7%) | 2,633 (61.3%) | 0 (NA%) | 3,586 (56.2%) | 834 (59%) | 7,080 (68.5%) |
| Age in categories (n/%): > 60 | 1,633 (48.8%) | 6,483 (30.8%) | 1,628 (37.9%) | 0 (NA%) | 2,772 (43.4%) | 571 (40.4%) | 3,159 (30.6%) |
| Number of persons who started the follow-up | 3,085 (92.1%) | 20,324 (96.5%) | 3,957 (92.2%) | 0 (NA%) | 5,988 (93.9%) | 1,276 (90.3%) | 9,857 (95.3%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 9,395 | 69,637 | 6,407 | 0 | 18,807 | 2,508 | 29,422 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 1 | NA | 3 | 1 | 4 |
| Number of people with vaccinations (n/%): 0 | 606 (18.1%) | 15,772 (74.9%) | 1,891 (44.1%) | 0 (NA%) | 1,438 (22.5%) | 522 (36.9%) | 1,280 (12.4%) |
| Number of people with vaccinations (n/%): 1 | 341 (10.2%) | 1,900 (9%) | 818 (19.1%) | 0 (NA%) | 462 (7.2%) | 262 (18.5%) | 803 (7.8%) |
| Number of people with vaccinations (n/%): 2 | 388 (11.6%) | 956 (4.5%) | 633 (14.7%) | 0 (NA%) | 754 (11.8%) | 198 (14%) | 982 (9.5%) |
| Number of people with vaccinations (n/%): 3 or more | 1,750 (52.3%) | 1,696 (8%) | 615 (14.3%) | 0 (NA%) | 3,334 (52.3%) | 294 (20.8%) | 6,792 (65.7%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Prevalences of comorbidities and comedications during the look-back period are presented in Table 63. Individuals with an immunocompromised status ranged from 35.7% (SIDAP) to 70.3% (VID). Malignancies accounted for 2.8% of the cohort in CPRD to 20.5 in SNDS. Individuals with psoriasis varied from 5.3% in BIFAP to 41.3% in SNDS. SNDS reports the highest prevalence of drug use across most therapeutic groups, with some exceptions. Drugs to treat mental health diseases and anti-epileptics were slightly higher in CPRD. Individuals associated with the usage of lipid-lowering drugs ranged from 18.3% (NHR) to 27.4% (VID). Individuals using cardiovascular medication were lowest in NHR (15.3%) and highest in BIFAP (48.3%). No NSAIDs were found in SNDS and PEDIANET but accounted for 36.7% to 57.5% of the rest of the databases.
Tumor necrosis factor (TNF) inhibitor users spanned from 0% in BIFAP, PEDIANET, and SIDIAP to 20.2% in SNDS.

*Table 63. Comorbidities and comedications in the PSA study cohort.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 3,348 | 21,070 | 4,292 | 0 | 6,380 | 1,413 | 10,338 |
| Immunocompromise status (n/%) | 1,239 (37%) | 9,051 (43%) | 3,018 (70.3%) | 0 (0%) | 2,277 (35.7%) | 897 (63.5%) | 6,897 (66.7%) |
| Malignancy (n/%) | 154 (4.6%) | 591 (2.8%) | 269 (6.3%) | 0 (0%) | 278 (4.4%) | 290 (20.5%) | 495 (4.8%) |
| Cardiocerebrovascular disease (n/%) | 1,659 (49.6%) | 7,926 (37.6%) | 1,977 (46.1%) | 0 (0%) | 2,947 (46.2%) | 686 (48.5%) | 1,741 (16.8%) |
| HIV (n/%) | < 5 | 7 (0%) | 23 (0.5%) | 0 (0%) | < 5 | < 5 | 9 (0.1%) |
| Inflammatory bowel disease (n/%) | 7 (0.2%) | 91 (0.4%) | 48 (1.1%) | 0 (0%) | 17 (0.3%) | 23 (1.6%) | 340 (3.3%) |
| Psoriasis (n/%) | 177 (5.3%) | 3,930 (18.7%) | 1,280 (29.8%) | 0 (0%) | 498 (7.8%) | 109 (7.7%) | 4,272 (41.3%) |
| Gout (n/%) | 22 (0.7%) | 407 (1.9%) | 130 (3%) | 0 (0%) | 64 (1%) | 13 (0.9%) | 280 (2.7%) |
| Immunostimulants (n/%) | 0 (0%) | 0 (0%) | < 5 | 0 (0%) | 0 (0%) | < 5 | 17 (0.2%) |
| Analgesics (n/%) | 1,736 (51.9%) | 7,819 (37.1%) | 2,405 (56%) | 0 (0%) | 3,121 (48.9%) | 1,252 (88.6%) | 4,685 (45.3%) |
| Systemic corticosteroids (n/%) | 896 (26.8%) | 3,082 (14.6%) | 981 (22.9%) | 0 (0%) | 1,610 (25.2%) | 761 (53.9%) | 2,847 (27.5%) |
| Antithrombotic agents (n/%) | 664 (19.8%) | 2,288 (10.9%) | 636 (14.8%) | 0 (0%) | 1,028 (16.1%) | 327 (23.1%) | 1,563 (15.1%) |
| Sex hormones (n/%) | 86 (2.6%) | 2,562 (12.2%) | 109 (2.5%) | 0 (0%) | 113 (1.8%) | 191 (13.5%) | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 1,487 (44.4%) | 7,483 (35.5%) | 2,430 (56.6%) | 0 (0%) | 2,663 (41.7%) | 1,071 (75.8%) | 4,590 (44.4%) |
| Diabetes medications (n/%) | 434 (13%) | 1,982 (9.4%) | 551 (12.8%) | 0 (0%) | 820 (12.9%) | 198 (14%) | 799 (7.7%) |
| Antibiotics (n/%) | 1,141 (34.1%) | 7,344 (34.9%) | 1,690 (39.4%) | 0 (0%) | 1,970 (30.9%) | 841 (59.5%) | 3,053 (29.5%) |
| Antiviral drugs (n/%) | 53 (1.6%) | 337 (1.6%) | 79 (1.8%) | 0 (0%) | 71 (1.1%) | 90 (6.4%) | 217 (2.1%) |
| Antimycotics (n/%) | 58 (1.7%) | 396 (1.9%) | 0 (0%) | 0 (0%) | 103 (1.6%) | 74 (5.2%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 1,458 (43.5%) | 7,743 (36.7%) | 2,409 (56.1%) | 0 (0%) | 2,977 (46.7%) | 0 (0%) | 5,945 (57.5%) |
| Drug to treat mental health diseases (n/%) | 724 (21.6%) | 6,239 (29.6%) | 905 (21.1%) | 0 (0%) | 1,301 (20.4%) | 347 (24.6%) | 1,566 (15.1%) |
| Lipid lowering drugs (n/%) | 863 (25.8%) | 4,420 (21%) | 1,177 (27.4%) | 0 (0%) | 1,459 (22.9%) | 304 (21.5%) | 1,887 (18.3%) |
| Cardiovascular medication (n/%) | 1,618 (48.3%) | 7,880 (37.4%) | 1,968 (45.9%) | 0 (0%) | 2,935 (46%) | 680 (48.1%) | 1,583 (15.3%) |
| Oncologic drugs (n/%) | 45 (1.3%) | 410 (1.9%) | 159 (3.7%) | 0 (0%) | 119 (1.9%) | 256 (18.1%) | 81 (0.8%) |
| Anti-epileptics (n/%) | 349 (10.4%) | 429 (2%) | 493 (11.5%) | 0 (0%) | 629 (9.9%) | 161 (11.4%) | 558 (5.4%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 303 (1.4%) | 634 (14.8%) | 0 (0%) | 0 (0%) | 285 (20.2%) | 765 (7.4%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.8.3 IRs of PSA flares

#### 10.8.3.1 IRs of PSA flares in the general population

The IR of the first flare up episode among PSA patients lies within the range of 232.4 flare cases per 1000 PY in CPRD to 541.1 per 1000 PY in SNDS. The IRs of the second flare up episode decreased in all databases in relation to the IRs of the first episode: from 136.8 flare cases per 1000 PY in SIDIAP to 335.2 per 1000 PY in SNDS. Finally, IRs of persons who develop a third flare-up episode also decreased in all databases in relation of the second flare: from 55.2 flare cases per 1000 PY in SIDIAP to 274.9 per 1000 PY in SNDS. An important number of PSA patients fulfilled the flare's criteria during the 90-days lag time from the cohort entry to the start of follow-up.

*Table 64. Background incidence rate of first, second, and third flare in the PSA cohort per 1,000 person-years (95% confidence interval).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 3,348 | 21,070 | 4,292 | 0 | 6,380 | 1,413 | 10,338 |
| Number of persons who started the follow-up | 3,050 | 20,164 | 3,868 | NA | 5,962 | 1,243 | 9,768 |
| Number of flares before entering follow-up | 1,611 | 9,085 | 2,431 | 0 | 3,186 | 950 | 5,918 |
| Number of persons who develop a first flare-up episode | 1,253 | 9,403 | 1,438 | NA | 2,588 | 625 | 4,209 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 269 (254.3-284.3) | 232.4 (227.7-237.1) | 380.2 (360.8-400.4) | NA | 281.8 (271-292.9) | 541.1 (499.5-585.3) | 320.9 (311.2-330.7) |
| Number of persons still in the study 90 days after first flare | 1,150 | 8,847 | 1,256 | NA | 2,507 | 549 | 3,919 |
| Number of persons who develop a second flare-up episode | 261 | 2,627 | 206 | NA | 542 | 177 | 918 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 146.6 (129.4-165.5) | 147 (141.4-152.7) | 206.1 (178.9-236.3) | NA | 136.8 (125.6-148.9) | 335.2 (287.6-388.4) | 161.8 (151.5-172.6) |
| Number of persons still in the study 90 days after second flare | 231 | 2,428 | 174 | NA | 522 | 149 | 842 |
| Number of persons who develop a third flare-up episode | 26 | 487 | 17 | NA | 45 | 35 | 134 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 84.6 (55.2-123.9) | 117.4 (107.2-128.3) | 156.2 (91-250) | NA | 55.2 (40.3-73.9) | 274.9 (191.5-382.3) | 124.4 (104.2-147.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.8.3.2 IRs of PSA flares stratified per age categories

Most of the people experiencing 1 to 3 episodes of PSA flares were adults, especially 18-59 years old. Very low cases were registered for 0-17-year-old individuals, especially for the second and third flare episodes. Overall, the incidence of flares decreased from the first episode to the second one and from the second one to the third for all the data sources <17 years old categories. For the 0-17-year-old category, the IRs per 1000 PY of the first flare ranged from 155.6 (BIFAP) to 531.7 (SNDS), the IRs of the second flare episodes

span from 0 (BIFAP) to 628.1 (SIDIAP) per 1000 PY, while the rates of the third flares were not available in most of the data sources as the number of persons still in the study 90 days after second flare were only a few (9 in CPRD to 0 in BIFAP, PEDIANET, and SNDS). For the 18-59-year-old category, the IRs per 1000 PY of the first flare ranged from 266.4 (CPRD) to 658 (SNDS), for the second flare episodes span from 148.4 (SIDIAP) to 391.5 (SNDS), and for the third flare episodes span from 59.1 (SIDIAP) to 283.7 (SNDS). For the ≥ 60 years category, the IRs per 1000 PY of the first flare ranged from 179 (CPRD) to 405.5 (SNDS), for the second flare episodes span from 111.7 (CPRD) to 248.3 (SNDS), and for the third flare episodes span from 48.6 (SIDIAP) to 255.2 (SNDS). Only in SNDS, the IRs of the third flares were slightly higher than the second flares in individuals ≥ 60 years old.

*Table 65. Background incidence rate of first, second, and third flare in the PSA cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | < 5 | 44 | < 5 | | 8 | < 5 | 31 |
| Number of persons who develop a first flare-up episode | 18-59 | 684 | 6523 | 924 | | 1541 | 407 | 2985 |
| Number of persons who develop a first flare-up episode | 60+ | 565 | 2836 | 510 | | 1039 | 216 | 1193 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 155.6 (42.4-398.3) | 329.7 (239.6-442.6) | 190.8 (52-488.5) | NA | 355.8 (153.6-701) | 531.7 (64.4-1920.5) | 305.3 (207.5-433.4) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 293.8 (272.2-316.7) | 266.4 (260-272.9) | 416.7 (390.3-444.5) | NA | 311.6 (296.3-327.6) | 658 (595.6-725.1) | 351.3 (338.8-364.2) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 245.1 (225.3-266.2) | 179 (172.5-185.7) | 330.4 (302.3-360.4) | NA | 246.4 (231.7-261.9) | 405.5 (353.2-463.4) | 264 (249.2-279.4) |
| Number of persons still in the study 90 days after first flare | 0-17 | < 5 | 38 | < 5 | | 7 | < 5 | 25 |
| Number of persons still in the study 90 days after first flare | 18-59 | 627 | 6,119 | 802 | | 1,500 | 353 | 2,768 |
| Number of persons still in the study 90 days after first flare | 60+ | 571 | 3,165 | 485 | | 1,135 | 210 | 1,320 |
| Number of persons who develop a second flare-up episode | 0-17 | 0 | 9 | < 5 | | < 5 | 0 | 7 |
| Number of persons who develop a second flare-up episode | 18-59 | 159 | 1,906 | 135 | | 344 | 127 | 687 |
| Number of persons who develop a second flare-up episode | 60+ | 102 | 712 | 70 | | 196 | 50 | 224 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 0 (0-460.3) | 157.5 (72-299) | 275.9 (7-1537) | NA | 628.1 (76.1-2269) | 0 (0-1639.1) | 260.7 (104.8-537.1) |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 160.4 (136.5-187.4) | 166.6 (159.2-174.2) | 217.8 (182.6-257.8) | NA | 148.4 (133.1-164.9) | 391.5 (326.4-465.8) | 175.6 (162.7-189.2) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 130.6 (106.5-158.6) | 111.7 (103.6-120.2) | 186.1 (145.1-235.2) | NA | 119.5 (103.4-137.5) | 248.3 (184.3-327.3) | 129.2 (112.8-147.3) |
| Number of persons still in the study 90 days after second flare | 0-17 | | 9 | < 5 | | < 5 | | 6 |
| Number of persons still in the study 90 days after second flare | 18-59 | 140 | 1,765 | 113 | | 332 | 105 | 631 |
| Number of persons still in the study 90 days after second flare | 60+ | 107 | 752 | 63 | | 218 | 48 | 260 |
| Number of persons who develop a third flare-up episode | 0-17 | | 0 | 0 | | 0 | | NR |
| Number of persons who develop a third flare-up episode | 18-59 | 20 | 368 | 12 | | 31 | 25 | NR |
| Number of persons who develop a third flare-up episode | 60+ | 6 | 119 | 5 | | 14 | 10 | NR |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | NA | 0 (0-393.7) | 0 (0-3428.4) | NA | 0 (0-1967) | NA | 531.3 (64.3-1,919.1) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 106.9 (65.3-165.1) | 127.6 (114.9-141.3) | 164.7 (85.1-287.7) | NA | 59.1 (40.1-83.8) | 283.7 (183.6-418.8) | 127.8 (104.1-155.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 49.9 (18.3-108.6) | 94.7 (78.5-113.4) | 143.1 (46.5-334.1) | NA | 48.6 (26.5-81.5) | 255.2 (122.4-469.3) | 109.4 (74.3-155.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.8.3.3 IRs of PSA stratified per gender

Across data sources, the number of females who developed a first, second, or third episode of PSA flares and their incidence was overall higher than that of males, except for the rates of second flares in NHR (almost equal across gender groups) and cases and rates of third flares in VID (higher in males) as shown in Table 66. These findings are in line with the reported evidence about PsA being a disease that mainly affects females (54). The IRs per 1000 PY of first PSA flares for females ranged from 254.3 (CPRD) to 581.7 (SNDS), while male rates moved from 209.8 (CPRD) to 494 (SNDS). The number of cases and the IRs per 1000 PY of second PSA flares were much lower than in the first episodes. Overall, the second PSA flares ranged from 151.9 (SIDIAP) to 371.2 (SNDS) per 1000 PY in females, while male rates moved from 120.7 (SIDIAP) to 283 (SNDS) per 1000 PY. The number of cases and the IRs per 1000 PY of third PSA flares were lower than the second episodes, except for males in VID. Overall, the IRS per 1000 PY of third PSA flares ranged from 56.3 (SIDIAP) to 275.3 (SNDS) in females, while male rates moved from 53.8 (SIDIAP) to 292.5 (VID).

*Table 66. Background incidence rate of first, second, and third flare in the PSA cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 673 | 5223 | 798 | | 1353 | 361 | 2357 |
| Number of persons who develop a first flare-up episode | M | 580 | 4180 | 640 | | 1235 | 264 | 1852 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 289.9 (268.4-312.7) | 254.3 (247.5-261.3) | 402.4 (375-431.4) | NA | 313.8 (297.3-331) | 581.7 (523.2-644.9) | 337.2 (323.7-351.1) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 248.1 (228.4-269.2) | 209.8 (203.5-216.3) | 355.7 (328.7-384.4) | NA | 253.5 (239.5-268) | 494 (436.2-557.4) | 302.2 (288.6-316.3) |
| Number of persons still in the study 90 days after first flare | F | 615 | 4922 | 683 | | 1318 | 319 | 2199 |
| Number of persons still in the study 90 days after first flare | M | 535 | 3925 | 573 | | 1189 | 230 | 1720 |
| Number of persons who develop a second flare-up episode | F | 150 | 1578 | 113 | | 311 | 116 | 513 |
| Number of persons who develop a second flare-up episode | M | 111 | 1049 | 93 | | 231 | 61 | 405 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 158.3 (134-185.8) | 161.6 (153.7-169.8) | 211 (173.9-253.7) | NA | 151.9 (135.5-169.8) | 371.2 (306.7-445.2) | 161.1 (147.4-175.6) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 133.3 (109.7-160.5) | 129.4 (121.7-137.4) | 200.5 (161.8-245.6) | NA | 120.7 (105.6-137.3) | 283 (216.5-363.6) | 162.8 (147.3-179.4) |
| Number of persons still in the study 90 days after second flare | F | 133 | 1456 | 90 | | 297 | 99 | 475 |
| Number of persons still in the study 90 days after second flare | M | 98 | 972 | 84 | | 225 | 50 | 367 |
| Number of persons who develop a third flare-up episode | F | 17 | 308 | < 5 | | 26 | 24 | 77 |
| Number of persons who develop a third flare-up episode | M | 9 | 179 | 13 | | 19 | 11 | 57 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 94.8 (55.3-151.9) | 124.3 (110.8-139) | 62.1 (16.9-159) | NA | 56.3 (36.8-82.5) | 275.3 (176.4-409.6) | 129 (101.8-161.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 70.2 (32.1-133.3) | 107.1 (92-124) | 292.5 (155.7-500.2) | NA | 53.8 (32.4-84) | 274.1 (136.8-490.5) | 118.6 (89.8-153.6) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.8.3.4 IRs of PSA in pregnant population

VID, SIDAP and NHR identified pregnant women among the PSA cohort population. BIFAP, CPRD, PEDIANET (adolescents up to 14 years of age) and SNDS did not run the pregnancy algorithm script to identify pregnancies in the databases. Twenty-six

persons who have at least one pregnancy after the start of follow-up were identified in VID, 68 in SIDIAP, and 184 in NHR. The IR of the first flare episode of PSA among pregnant population in VID was 193.4 (CI 95% 23.4 – 698.7), in SIDIAP was 320.7 (CI 95% 146.6-608.7), and in NHR was 130.7 (CI 95% 62.7-240.4). The number of persons who developed a second and third flare episodes while pregnant were very few. See Table 67 below.

*Table 67. Background IRs in pregnant population of flare episodes in the PSA cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 26 | 68 | NA | 184 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | < 5 | 9 | NA | 10 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 193.4 (23.4-698.7) | 320.7 (146.6-608.7) | NA | 130.7 (62.7-240.4) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | 8 | 16 | NA | 70 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | < 5 | NA | < 5 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 338.2 (8.6-1884.3) | 116.6 (3-649.8) | NA | 114.8 (23.7-335.5) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | < 5 | < 5 | NA | 13 |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | 0 | 0 | NA | < 5 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-4812) | 0 (0-8636.9) | NA | 183.2 (4.6-1020.6) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.8.4 Six- and twelve-months cumulative incidence of flares of PSA

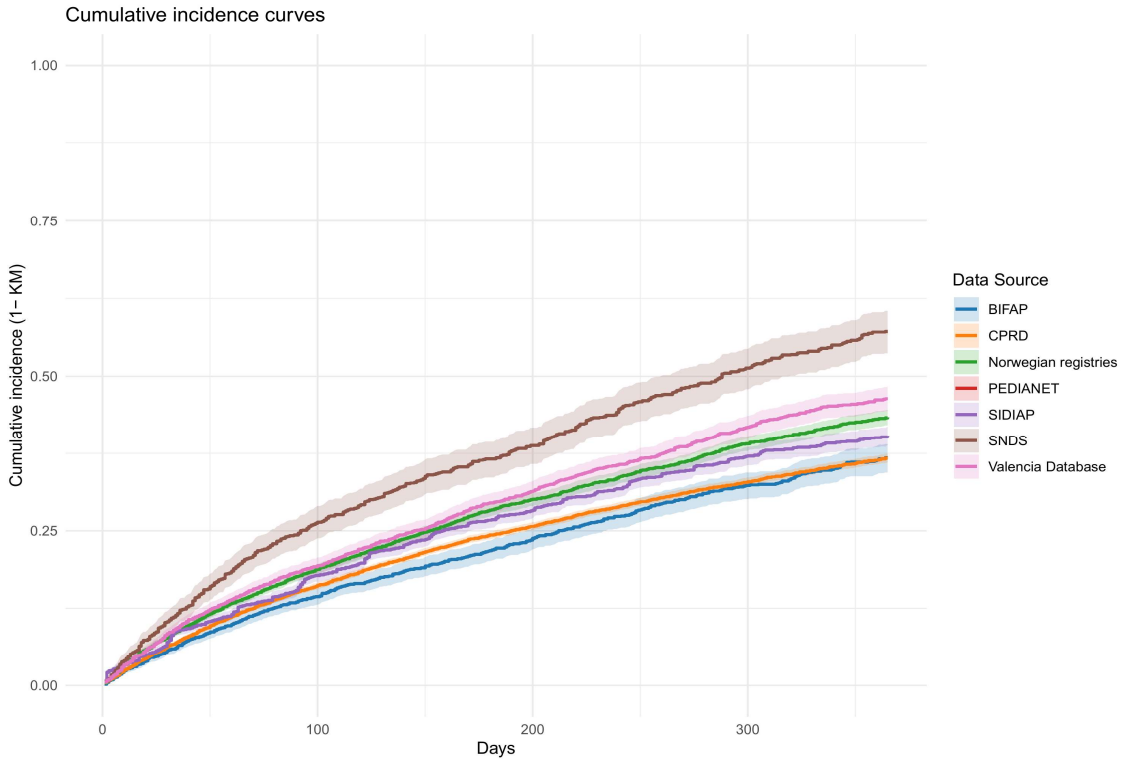
Table 68 shows the 6- and 12-months cumulative incidence of the first flare episode of PSA. The 6-month risk of a first flare in PSA patients was 29.5% in VID, 26.7% in SIDIAP, 36.6% in SNDS, 24.3% in CPRD, 21.8% in BIFAP and 28.3% in NHR. The one-year risk of having a flare was 36.7% in CPRD, 46.4% in VID, 40.4% in SIDIAP, 57.2% in SNDS, 36.8% in BIFAP and 43.4% in NHR. A cumulative incidence curve for PSA is presented in Figure 18.

*Table 68. Six- and twelve-months cumulative incidence of flares of PSA (95% confidence interval)*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|
| 180 | 0.283 (0.273-0.293) | 0.295 (0.279-0.31) | 0.267 (0.254-0.279) | 0.218 (0.201-0.234) | 0.366 (0.336-0.394) | 0.243 (0.236-0.249) |
| 365 | 0.434 (0.421-0.446) | 0.464 (0.444-0.483) | 0.404 (0.388-0.419) | 0.368 (0.344-0.39) | 0.572 (0.537-0.605) | 0.367 (0.36-0.374) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 18. Cumulative incidence curve of PSA.*



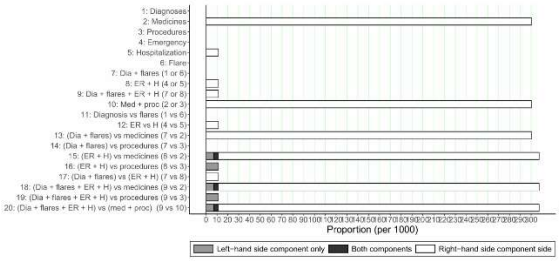

### 10.8.5 Other analyses

#### 10.8.5.1 Component analysis

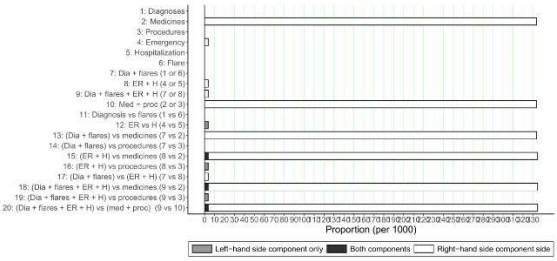
MED was the highest component (>94%) of the 12-month cumulative incidence of the first PA flare episode in all data sources (see Figure 19). The remaining cases were identified via H (SNDS, SIDIAP and BIFAP) or ER (VID). The overlapping between MED and the other components (H or ER) ranged from 0.1% (SIDIAP) to 11.3% (SNDS).

*Figure 19. Component Analysis for PSA*

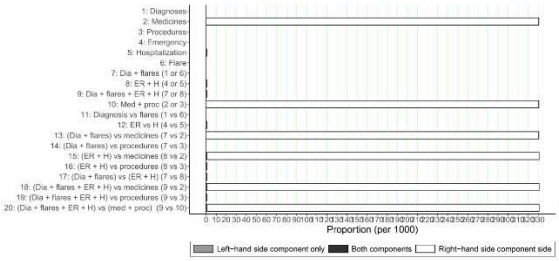
**BIFAP**



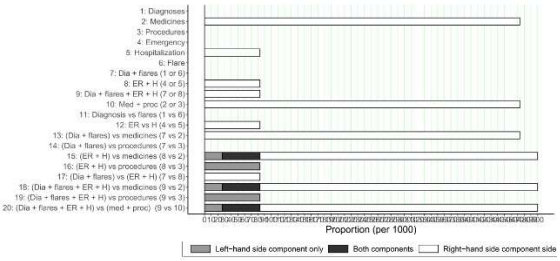

**VID**



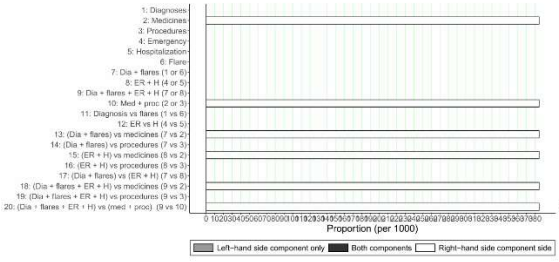

**SIDIAP**



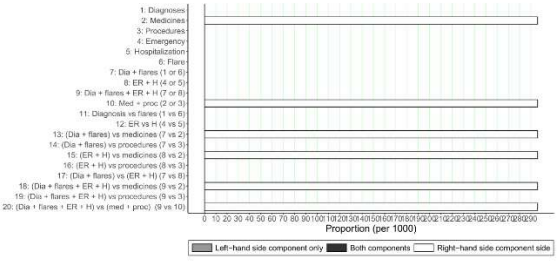

**SNDS**




**NHR**




**CPRD**



## 10.9 POLYARTERITIS NODOSUM (PAN)

### 10.9.1 Attrition of the study population

In BIFAP, 450 PAN subjects entered the disease cohort, 90.7% (n=408) of them started the follow up. In the CPRD database, 199 PAN subjects entered the cohort and 94.4% (n=188) of them started the follow up. In VID, 439 subjects with PAN were retained after exclusion criteria, 96.5% (n=424) of them started the follow up. In SIDIAP, 331 subjects with PAN entered the cohort, and 89.7% (n=297) of them started the follow up. In the French database SNDS, 141 PAN patients became part of the study cohort, 91.4% (n=129) of them started the follow-up. In NHR, 201 subjects entered the PAN incident cohort, and 90.5% (n=182) started the follow up. Finally, in the Italian PEDIANET database (paediatric population), there were no PAN cases identified. See Table 69 below.

*Table 69. Characteristics of the study PAN cohort*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 549 | 281 | 598 | 0 | 388 | 196 | 252 |
| Disease codes found during lookback | 99 | 82 | 159 | 0 | 57 | 55 | 51 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Polyarteritis nodosa | 450 | 199 | 439 | NA | 331 | 141 | 201 |
| Persons dying before entrance in the follow-up | 15 | NR | 6 | 0 | 17 | 5 | 5 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 27 | NR | 9 | 0 | 17 | 7 | 14 |
| Persons entering follow-up | 408 | 188 | 424 | NA | 297 | 129 | 182 |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.9.2 Characteristics of the study cohort

The total PAN study cohort who started the follow up across databases comprised 1,628 subjects. The total follow-up time ranged between 226 PY in SNDS to 1,171 PY in BIFAP. Across data sources, between 52.6 to 64% of the cohort population were females. The male-to-female sex ratio in AIH incident cases across databases was 72 males to every 100 females. The median age (interquartile range 50) was between 56- to 65-year-old across data sources,. Data about median age of people with PAN diagnosis are in line with other publications. However, it is reported to have a male preponderance globally (55,56).
The percentage of people with at least 3 vaccinations was from 7% in CPRD to 55.2% in NHR. See Table 70.

*Table 70. Characteristics of the PAN study cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 450 | 199 | 439 | 0 | 331 | 141 | 201 |
| Female (n/%) | 258 (57.3%) | 119 (59.8%) | 281 (64%) | NA | 174 (52.6%) | 85 (60.3%) | 114 (56.7%) |
| Male (n/%) | 192 (42.7%) | 80 (40.2%) | 158 (36%) | NA | 157 (47.4%) | 56 (39.7%) | 87 (43.3%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 46 | 44 | 39 | NA | 50 | 41 | 39 |
| Age in year (IQR): PCT 50 | 60 | 58 | 56 | NA | 65 | 62 | 61 |
| Age in year (IQR): PCT 75 | 74 | 71 | 72 | NA | 77 | 72 | 72 |
| Age in categories (n/%): < 18 | 14 (3.1%) | 8 (4%) | 56 (12.8%) | NA | 13 (3.9%) | 7 (5%) | 20 (10%) |
| Age in categories (n/%): 18-59 | 204 (45.3%) | 98 (49.2%) | 180 (41%) | NA | 121 (36.6%) | 59 (41.8%) | 77 (38.3%) |
| Age in categories (n/%): > 60 | 232 (51.6%) | 93 (46.7%) | 203 (46.2%) | NA | 197 (59.5%) | 75 (53.2%) | 104 (51.7%) |
| Number of persons who started the follow-up | 408 (90.7%) | 188 (94.5%) | 424 (96.6%) | NA | 297 (89.7%) | 129 (91.5%) | 182 (90.5%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 1,171 | 669 | 859 | NA | 896 | 226 | 495 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 1 | NA | 3 | 1 | 3 |
| Number of people with vaccinations (n/%): 0 | 96 (21.3%) | 142 (71.4%) | 179 (40.8%) | NA | 71 (21.5%) | 61 (43.3%) | 31 (15.4%) |
| Number of people with vaccinations (n/%): 1 | 34 (7.6%) | 24 (12.1%) | 77 (17.5%) | NA | 22 (6.6%) | 21 (14.9%) | 14 (7%) |
| Number of people with vaccinations (n/%): 2 | 41 (9.1%) | 8 (4%) | 81 (18.5%) | NA | 32 (9.7%) | 25 (17.7%) | 26 (12.9%) |
| Number of people with vaccinations (n/%): 3 or more | 237 (52.7%) | 14 (7%) | 87 (19.8%) | NA | 172 (52%) | 22 (15.6%) | 111 (55.2%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Prevalence of comorbidities and comedications during the look-back period in the PAN study cohort are described in Table 71. Twenty-two to 33% of the PAN population had a diagnosis implying an immunosuppressive status. In SNDS, the prevalence of malignancy was as high as 14.9%, while the lowest was reported in CPRD (5%). Prevalence of chronic renal disease accounted for 3.5% (CPRD) to 14.2% (SIDIAP). Immunosuppressants medications were used between 39.2% (VID) and 64.5% (SNDS),

and systemic corticosteroids between 33.5% (VID) and 59.6% (SNDS). Overall, a higher prevalence of co-medication use was observed in SNDS, with some exceptions as follows. Use of diabetes medications span from 10% (NHR) to 14.5% (SIDIAP). Prevalence of antibiotic use was between 46.7% (SIDIAP) to 67.4% (SNDS).
Non-steroidal anti-inflammatory drugs were reported to be used from 13.6% (CPRD) to 39.6% (VID) while no data were available for SNDS. Lipid lowering drugs prevalence were lower in NHR (20.4%) and higher in VID and SIDIAP (>30%).

*Table 71 Comorbidities and comedications in PAN study cohort.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 450 | 199 | 439 | 0 | 331 | 141 | 201 |
| Immunocompromise status (n/%) | 101 (22.4%) | 50 (25.1%) | 130 (29.6%) | 0 (0%) | 100 (30.2%) | 47 (33.3%) | 66 (32.8%) |
| Malignancy (n/%) | 26 (5.8%) | 10 (5%) | 15 (3.4%) | 0 (0%) | 25 (7.6%) | 21 (14.9%) | 14 (7%) |
| HIV (n/%) | < 5 | < 5 | 0 (0%) | 0 (0%) | < 5 | < 5 | 0 (0%) |
| Chronic renal disease (n/%) | 51 (11.3%) | 7 (3.5%) | 36 (8.2%) | 0 (0%) | 47 (14.2%) | 9 (6.4%) | 14 (7%) |
| Hepatitis C (n/%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | < 5 | 0 (0%) |
| Hepatitis B (n/%) | < 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Immunostimulants (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | < 5 | < 5 |
| Analgesics (n/%) | 243 (54%) | 76 (38.2%) | 263 (59.9%) | 0 (0%) | 186 (56.2%) | 124 (87.9%) | 96 (47.8%) |
| Systemic corticosteroids (n/%) | 175 (38.9%) | 68 (34.2%) | 147 (33.5%) | 0 (0%) | 151 (45.6%) | 84 (59.6%) | 91 (45.3%) |
| Antithrombotic agents (n/%) | 133 (29.6%) | 50 (25.1%) | 125 (28.5%) | 0 (0%) | 117 (35.3%) | 69 (48.9%) | 68 (33.8%) |
| Sex hormones (n/%) | 8 (1.8%) | 18 (9%) | < 5 | 0 (0%) | 5 (1.5%) | 8 (5.7%) | 0 (0%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 188 (41.8%) | 84 (42.2%) | 172 (39.2%) | 0 (0%) | 161 (48.6%) | 91 (64.5%) | 94 (46.8%) |
| Diabetes medications (n/%) | 65 (14.4%) | 28 (14.1%) | 53 (12.1%) | 0 (0%) | 48 (14.5%) | 16 (11.3%) | 20 (10%) |
| Antibiotics (n/%) | 225 (50%) | 103 (51.8%) | 236 (53.8%) | 0 (0%) | 155 (46.8%) | 95 (67.4%) | 98 (48.8%) |
| Antiviral drugs (n/%) | 12 (2.7%) | 7 (3.5%) | 7 (1.6%) | 0 (0%) | < 5 | 10 (7.1%) | 6 (3%) |
| Antimycotics (n/%) | 12 (2.7%) | 6 (3%) | 0 (0%) | 0 (0%) | < 5 | 11 (7.8%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 121 (26.9%) | 27 (13.6%) | 174 (39.6%) | 0 (0%) | 87 (26.3%) | 0 (0%) | 59 (29.4%) |
| Drug to treat mental health diseases (n/%) | 105 (23.3%) | 55 (27.6%) | 102 (23.2%) | 0 (0%) | 86 (26%) | 41 (29.1%) | 27 (13.4%) |
| Lipid lowering drugs (n/%) | 117 (26%) | 56 (28.1%) | 132 (30.1%) | 0 (0%) | 103 (31.1%) | 35 (24.8%) | 41 (20.4%) |
| Cardiovascular medication (n/%) | 248 (55.1%) | 113 (56.8%) | 231 (52.6%) | 0 (0%) | 204 (61.6%) | 89 (63.1%) | 52 (25.9%) |
| Oncologic drugs (n/%) | 8 (1.8%) | 8 (4%) | 7 (1.6%) | 0 (0%) | 10 (3%) | 16 (11.3%) | < 5 |
| Anti-epileptics (n/%) | 63 (14%) | < 5 | 63 (14.4%) | 0 (0%) | 62 (18.7%) | 30 (21.3%) | 20 (10%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | < 5 | < 5 | 0 (0%) | 0 (0%) | 5 (3.5%) | < 5 |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.9.3 IRs of PAN flares

#### 10.9.3.1 IRs of PAN flares in the general population

No individuals who developed a first PAN flare episode were observed in CPRD. Evident variability was observed for the IR of the PAN flare episodes across data sources. In BIFAP, 63 subjects had a first flare-up with an IR of 80.9 per 1000 PY (CI 95% 62.1-103.5). In VID, 27 persons developed a first flare-up episode, leading to an IR of 38.4 per 1,000 PY (CI 95% 25.3-55.8). In SIDIAP, 52 patients developed a first flare-up episode accounting for an IR of 88.8 per 1000 PY (CI 95% 66.3-116.4). In SNDS, 23 subjects flared-up, leading to an IR of first flare episode of 142.9 per 1000 PY (CI 95% 90.6-214.4). Finally, in NHR, 36 patients developed a first flare, leading to an IR of 131.7 per 1000 PY (CI 95% 92.3-182.4).
Five, 8, 9 and 9 episodes of second flares were detected in SIDIAP, BIFAP, SNDS and NHR, respectively, while <5 episodes were detected in VID.
The third flare episode was <5 in all data sources, with small (<9 individuals) cohorts for this last episode. See Table 72 below.

*Table 72. Background incidence rate of first, second, and third flare in the PAN cohort, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 450 | 199 | 439 | 0 | 331 | 141 | 201 |
| Number of persons who started the follow-up | 407 | 188 | 423 | NA | 296 | 127 | 176 |
| Number of flares before entering follow-up | 75 | 0 | 80 | NA | 61 | 45 | 65 |
| Number of persons who develop a first flare-up episode | 63 | 0 | 27 | NA | 52 | 23 | 36 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 80.9 (62.1-103.5) | 0 (0-5.7) | 38.4 (25.3-55.8) | NA | 88.8 (66.3-116.4) | 142.9 (90.6-214.4) | 131.7 (92.3-182.4) |
| Number of persons still in the study 90 days after first flare | 58 | NA | 25 | NA | 49 | 20 | 36 |
| Number of persons who develop a second flare-up episode | 8 | NA | < 5 | NA | 5 | 9 | 9 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 88.8 (38.3-174.9) | NA | 75.5 (9.1-272.6) | NA | 61 (19.8-142.3) | 625.1 (285.8-1186.6) | 172.2 (78.7-326.9) |
| Number of persons still in the study 90 days after second flare | 7 | NA | < 5 | NA | 5 | 6 | 8 |
| Number of persons who develop a third flare-up episode | < 5 | NA | 0 | NA | < 5 | < 5 | < 5 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 227.6 (27.6-822.1) | NA | 0 (0-12030) | NA | 659 (179.6-1687.3) | 1808.2 (372.9-5284.2) | 284.3 (58.6-830.9) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.9.3.2 IRs of PAN flares stratified per age categories

Most of the people experiencing 1 episode of PAN flares were adults, especially 18-59 years old. Low cases (<5) were registered for 0-17-year-old individuals for all flares (first, second, third) cases. No cases were observed in CPRD. For the 0-17-year-old category, the IRs per 1000 PY of the first flare ranged from 9.8 (VID) to 473.7 (SNDS), while the rates of the second and third flares were not available in most of the data sources as the number of persons still in the study 90 days after second flare was only a few (<5). For the 18-59-year-old category, the IRs per 1000 PY of the first flare ranged from 52.4 (VID) to 216.4 (NHR), for the second flare episodes span from 56.5 (SIDIAP) to 443.7 (SNDS), while the number of persons still in the study 90 days after second flare was only a few (<5 or none) across all data sources. For the ≥ 60 years category, the IRs per 1000 PY of the first flare ranged from 33.7 (VID) to 101.3 (NHR), for the second flare episodes spanned from 19.8 (BIFAP) to 603.1 (SNDS), while the number of persons still in the study 90 days after the second flare was only a few (<5 or none) across all data sources. Overall, the incidence of flares seems to increase from the first episode to the second one in adults. However, both the first flare cohorts and those in the study 90 days after the first flare are very small.

*Table 73. Background incidence rate of first, second, and third flare in the PAN cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | < 5 | 0 | < 5 | 0 | < 5 | < 5 | NR |
| Number of persons who develop a first flare-up episode | 18-59 | 38 | 0 | 16 | NA | 24 | 12 | NR |
| Number of persons who develop a first flare-up episode | 60+ | 24 | 0 | 10 | NA | 24 | 8 | NR |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 35.9 (0.9-199.8) | 0 (0-160.5) | 9.8 (0.2-54.7) | NA | 167 (45.5-427.6) | 473.7 (97.7-1384.5) | 46.8 (5.7-169.2) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 102.8 (72.7-141.1) | 0 (0-12.3) | 52.4 (30-85.2) | NA | 108.2 (69.3-161) | 173.1 (89.5-302.4) | 216.4 (132.2-334.2) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 62.9 (40.3-93.6) | 0 (0-11.5) | 33.7 (16.2-62) | NA | 70.6 (45.2-105) | 93.7 (40.5-184.7) | 101.3 (55.4-170) |
| Number of persons still in the study 90 days after first flare | 0-17 | < 5 | | < 5 | NA | < 5 | < 5 | NR |
| Number of persons still in the study 90 days after first flare | 18-59 | 31 | | 12 | NA | 22 | 10 | NR |
| Number of persons still in the study 90 days after first flare | 60+ | 28 | | 12 | NA | 28 | 8 | NR |
| Number of persons who develop a second flare-up episode | 0-17 | 0 | | 0 | NA | < 5 | < 5 | < 5 |
| Number of persons who develop a | 18-59 | 7 | | < 5 | NA | < 5 | < 5 | 5 |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| second flare-up episode | | | | | | | | |
| Number of persons who develop a second flare-up episode | 60+ | < 5 | | 0 | NA | < 5 | < 5 | < 5 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 0 (0-1105.3) | NA | 0 (0-1550.5) | NA | 762.5 (19.3-4248.5) | 4902.7 (593.7-17710.2) | 509.4 (12.9-2838.3) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 192.7 (77.5-397.1) | NA | 208.2 (25.2-752.2) | NA | 56.5 (6.8-204) | 443.7 (120.9-1136) | 148.8 (48.3-347.2) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 19.8 (0.5-110.5) | NA | 0 (0-254.1) | NA | 44.2 (5.3-159.5) | 603.1 (124.4-1762.4) | 179.6 (37-524.9) |
| Number of persons still in the study 90 days after second flare | 0-17 | | | | | < 5 | < 5 | < 5 |
| Number of persons still in the study 90 days after second flare | 18-59 | 7 | | < 5 | | < 5 | < 5 | 5 |
| Number of persons still in the study 90 days after second flare | 60+ | | | | | < 5 | < 5 | < 5 |
| Number of persons who develop a third flare-up episode | 0-17 | | | | | 0 | < 5 | < 5 |
| Number of persons who develop a third flare-up episode | 18-59 | < 5 | | 0 | | < 5 | < 5 | < 5 |
| Number of persons who develop a third flare-up episode | 60+ | | | | | < 5 | 0 | < 5 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | NA | NA | NA | NA | 0 (0-24060.1) | 2,666.1 (67.5-14854.3) | 2,200.3 (55.7-12,259.3) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 227.6 (27.6-822.1) | NA | 0 (0-12030) | NA | 781 (161.1-2,282.4) | 1,702.8 (206.2-6,151.1) | 124.4 (3.1-693.1) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | NA | NA | NA | NA | 481.9 (12.2-2,684.8) | 0 (0-33,684.1) | 485.7 (12.3-2,706.2) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.9.3.3 IRs of PAN flares stratified per gender

Across data sources, the number of females who developed a first episode of PAN flares was slightly higher than that of males. However, the flare-up cohorts accounted for very few individuals (<35) across data sources and gender categories. No cases were reported in CPRD. The IRs per 1000 PY of first PAN flares for females ranged from 39.1 (VID) to 148.3 (SNDS), while male rates moved from 37.3 (VID) to 145 (NHR). Overall, rate values were comparable between gender categories, slightly higher for males in BIFAP and NHR, and vice-versa for the other data sources. The number of persons still in the

study 90 days after the first or second flare episode was low, as well as the cases of second and third flares (<5) across all data sources.

*Table 74. Background incidence rate of first, second, and third flare in the PAN cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 34 | 0 | 17 | | 31 | 15 | 19 |
| Number of persons who develop a first flare-up episode | M | 29 | 0 | 10 | | 21 | 8 | 17 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 78.1 (54.1-109.1) | 0 (0-9.3) | 39.1 (22.7-62.5) | NA | 99.1 (67.3-140.7) | 148.3 (83-244.6) | 121.7 (73.3-190.1) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 84.4 (56.5-121.2) | 0 (0-14.9) | 37.3 (17.9-68.6) | NA | 77 (47.6-117.7) | 133.7 (57.7-263.3) | 145 (84.5-232.2) |
| Number of persons still in the study 90 days after first flare | F | 29 | | 16 | | 30 | 13 | 19 |
| Number of persons still in the study 90 days after first flare | M | 29 | | 9 | | 19 | 7 | 17 |
| Number of persons who develop a second flare-up episode | F | < 5 | | < 5 | | < 5 | 5 | NR |
| Number of persons who develop a second flare-up episode | M | < 5 | | 0 | | < 5 | < 5 | NR |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 96.1 (26.2-246.1) | NA | 104.6 (12.7-377.8) | NA | 44 (5.3-159.1) | 617.6 (200.5-1,441.3) | 202 (74.1-439.7) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 82.5 (22.5-211.2) | NA | 0 (0-500.1) | NA | 81.9 (16.9-239.5) | 634.7 (172.9-1625) | 132.9 (27.4-388.5) |
| Number of persons still in the study 90 days after second flare | F | < 5 | | < 5 | | < 5 | < 5 | NR |
| Number of persons still in the study 90 days after second flare | M | < 5 | | | | < 5 | < 5 | NR |
| Number of persons who develop a third flare-up episode | F | < 5 | | 0 | | < 5 | < 5 | < 5 |
| Number of persons who develop a third flare-up episode | M | 0 | | | | < 5 | 0 | < 5 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 519.2 (62.9-1,875.5) | NA | 0 (0-12030) | NA | 633 (76.7-2,286.7) | 5707 (1,176.9-16,678.4) | 206.5 (25-745.8) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 0 (0-747.3) | NA | NA | NA | 687.2 (83.2-2,482.4) | 0 (0-3254.5) | 1,155.9 (29.3-6,440) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.9.3.4 IRs of PAN flares in pregnant population

VID, SIDIAP, and NHR identified <5 pregnant women who have at least one pregnancy after the start of follow-up for the PAN cohort population, with no cases of flares. BIFAP, CPRD, PEDIANET (adolescents up to 14 years of age) and SNDS did not run the pregnancy algorithm. See Table 75.

*Table 75 Background IR in pregnant population of first, second, and third flare in the PAN cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | < 5 | < 5 | NA | < 5 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 0 | 0 | NA | 0 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-5758) | 0 (0-2026.1) | NA | 0 (0-4403.1) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | NA | NA | NA | < 5 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | NA | NA | NA | 0 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | NA | NA | 0 (0-5263.1) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | NA | NA | NA | NA |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | NA | NA | NA | NA |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | NA | NA | NA | NA |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

## 10.9.4 Six- and twelve-months cumulative incidence of flares of PAN

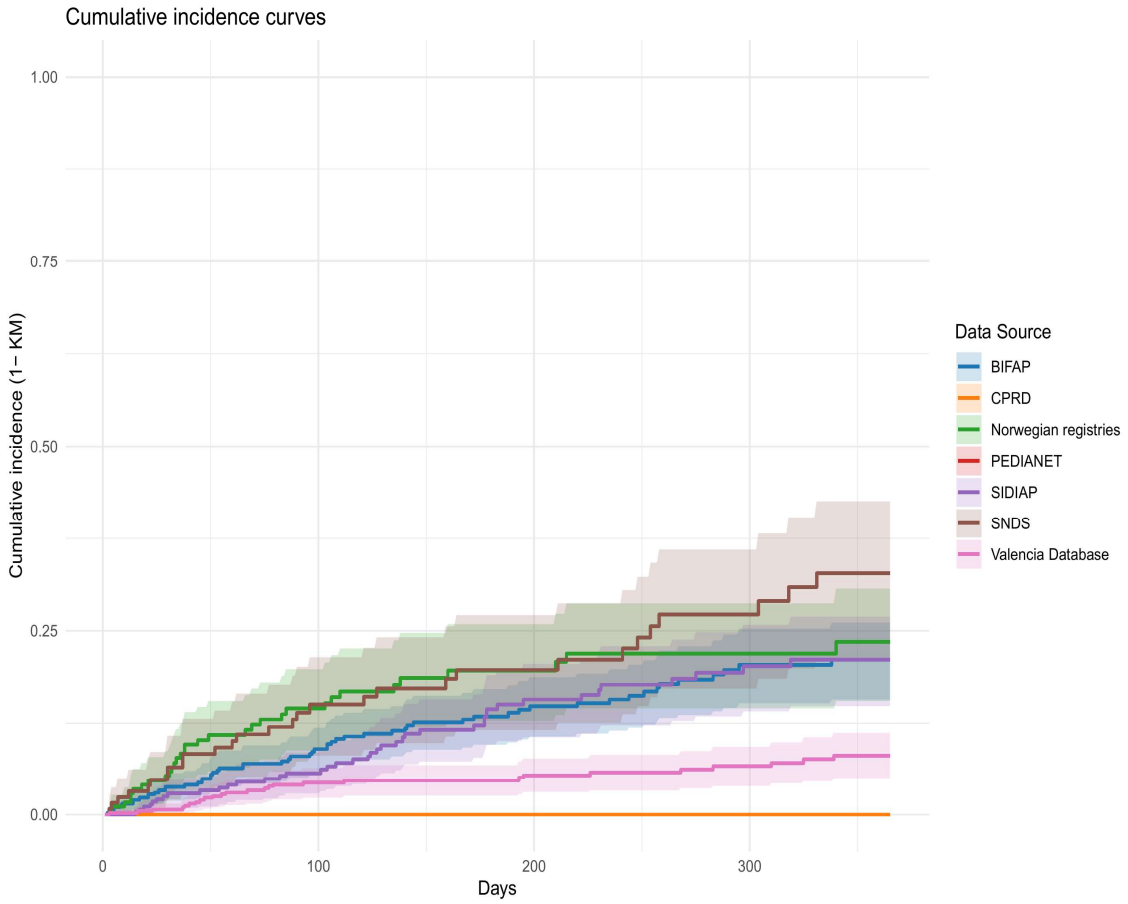
Table 76 shows the 6- and 12-months cumulative incidence of the first flare episode of PAN. The 6-month risk of a first flare in PAN patients was 4.7% for VID, 14.4% for SIDAP, 13,4% in BIFAP, 19.7% for SNDS, and 19.6% for NHR. The 12-month risk of a flare in PAN patients was 8.1% in VID, 21.1% in SIDAP-ES, 21.1% in BIFAP, 32.8% in SNDS, and 23.5% in NHR. The cumulative incidence curve is represented in Figure 20.

*Table 76. Six- and twelve-months cumulative incidence of flares of PAN (95% confidence interval)*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|
| 180 | 0.196 (0.128-0.259) | 0.047 (0.026-0.068) | 0.144 (0.096-0.19) | 0.134 (0.096-0.171) | 0.197 (0.116-0.271) | 0 (0-0) |
| 365 | 0.235 (0.155-0.307) | 0.081 (0.05-0.112) | 0.211 (0.148-0.269) | 0.211 (0.157-0.261) | 0.328 (0.213-0.426) | 0 (0-0) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 20. Cumulative incidence curve of PAN.*

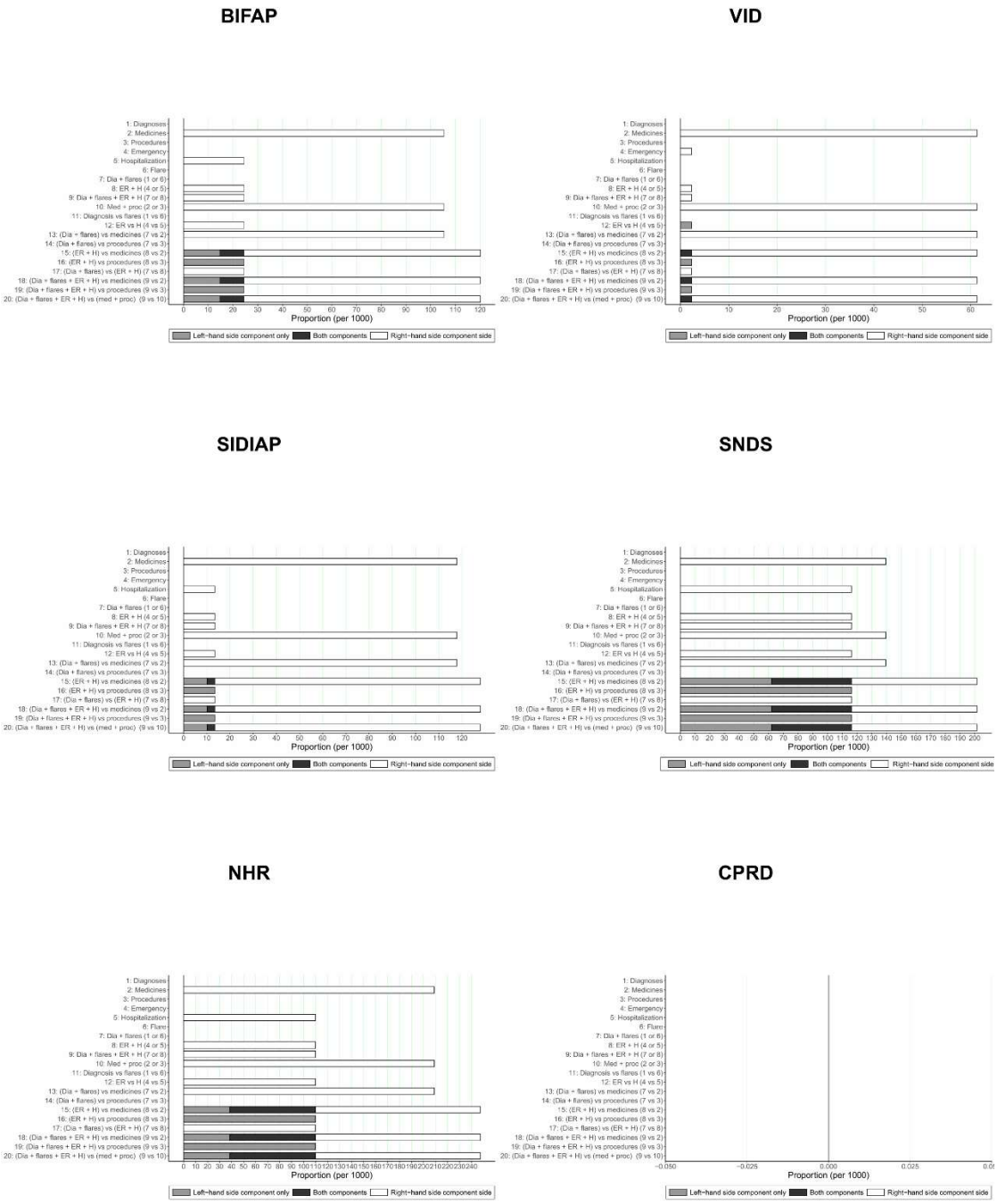



### 10.9.5 Other analyses

#### 10.9.5.1 Component analysis

Considering the components used to identify PAN flares (see Figure 21), it was found that MED had the highest 12-month cumulative incidence of first episodes among the five available data sources. This incidence ranged from 69.2% (SNDS) to 100% (VID). A significant number of remaining cases were identified through H (NHR, SIDIAP, BIFAP, and SNDS), with a smaller contribution from ER (VID). The overlapping identification of cases through MED and H or ER ranged from 2.7 % (SIDIAP) to 28.9% (NHR).

*Figure 21. Component Analysis for PAN*



## 10.10 ULCERATIVE COLITIS (UC)

### 10.10.1 Attrition of the study population

In the BIFAP database, 10,273 persons entered the UC cohort and 9,603 started follow up. In CPRD, 33,833 UC subjects entered the disease cohort and 32,425 started the follow up. In VID, 7,808 subjects with UC were identified, 93.2% (n=7,274) of them started the follow up. In SIDIAP, 11,584 subjects with UC entered the cohort, and 92.3% (n=10,696) of them started the follow up. In the French database SNDS, 7,403 UC patients became part of the study cohort, 91.3% (n=6,760) of them started the follow-up. In NHR, 16,132 subjects entered the UC incident cohort, and 95.4% (n=15,388) started the follow up. Finally, In the Italian PEDIANET database (paediatric population), <5 UC cases were identified and entered follow up. See Table 77.

*Table 77. Characteristics of the study UC cohort*

| Exclusion criteria | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total persons in the data instance | 22,580,036 | 26,546,692 | 5,371,422 | 46,392 | 7,553,433 | 7,484,958 | 5,824,950 |
| Sex or birthdate not defined | 0 | 0 | 0 | 0 | 0 | 3,270 | 880 |
| Birthdate absurd | 105 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death date incomplete | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| No observation periods, or observation periods lacking required data | 10,359,326 | 0 | 24,859 | 0 | 0 | 79 | 0 |
| Observation periods invalid (start after ending) | 0 | 266 | 1,544 | 0 | 0 | < 5 | 0 |
| Observation periods shorter than lookback (365 days) | 582,134 | 2,974,872 | 228,777 | 1,470 | 230,032 | 377 | 106,223 |
| Exit from data source before 1 Jan 2017 | 222,782 | 0 | 21,161 | 0 | 441,072 | 1,522 | 8,620 |
| Disease codes identified after study entry | 15,726 | 48,587 | 16,457 | < 5 | 13,502 | 12,397 | 33,057 |
| Disease codes found during lookback | 5,453 | 14,754 | 8,649 | < 5 | 1,918 | 4,994 | 16,925 |
| Other criteria suggesting the disease is present during lookback | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cohort of Ulcerative colitis | 10,273 | 33,833 | 7,808 | < 5 | 11,584 | 7,403 | 16,132 |
| Persons dying before entrance in the follow-up | 203 | 116 | 121 | 0 | 327 | 149 | 45 |
| Persons leaving alive the cohort before entering the follow-up (censoring) | 467 | 1,292 | 413 | 0 | 561 | 494 | 699 |
| Persons entering follow-up | 9,603 | 32,425 | 7,274 | < 5 | 10,696 | 6,760 | 15,388 |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.10.2 Characteristics of the study cohort

The total study population who started the follow up across databases was 82,146. The total follow-up time ranged between 12,551 PY in VID to 107,300 PY in CPRD, while in PEDIANET was 8 PY. Across data sources, between 48 to 51% of the cohort population were females. The male-to-female sex ratio in UC incident cases across databases was 98 females to every 100 males. The median age (interquartile range 50) was between 43- to 55-year-old across data sources, except for PEDIANET (3.5 years old). These data are aligned with previous demographic knowledge about UC in the general population, especially for the almost equal distribution of UC between males and females (57). The percentage of people with at least 3 vaccinations was from 5.9% in CPRD to 59.8% in NHR. See Table 78.

*Table 78. Characteristics of the study UC cohort.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 10,273 | 33,833 | 7,808 | < 5 | 11,584 | 7,403 | 16,132 |
| Female (n/%) | 5,092 (49.6%) | 16,471 (48.7%) | 3,969 (50.8%) | 0 (0%) | 5,850 (50.5%) | 3,668 (49.5%) | 7,744 (48%) |
| Male (n/%) | 5,181 (50.4%) | 17,362 (51.3%) | 3,839 (49.2%) | < 5 | 5,734 (49.5%) | 3,735 (50.5%) | 8,388 (52%) |
| Other (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Age in year (IQR): PCT 25 | 35.00 | 34.00 | 39.00 | 2.75 | 39.00 | 32.00 | 28.00 |
| Age in year (IQR): PCT 50 | 51.0 | 49.0 | 51.0 | 3.5 | 55.0 | 48.0 | 43.0 |
| Age in year (IQR): PCT 75 | 66.00 | 64.00 | 64.00 | 4.25 | 70.00 | 64.00 | 59.00 |
| Age in categories (n/%): < 18 | 794 (7.7%) | 1276 (3.8%) | 308 (3.9%) | < 5 | 355 (3.1%) | 350 (4.7%) | 940 (5.8%) |
| Age in categories (n/%): 18-59 | 5,882 (57.3%) | 21,753 (64.3%) | 4,952 (63.4%) | 0 (0%) | 6,406 (55.3%) | 4,722 (63.8%) | 11,331 (70.2%) |
| Age in categories (n/%): > 60 | 3,597 (35%) | 10,804 (31.9%) | 2,548 (32.6%) | 0 (0%) | 4,823 (41.6%) | 2,331 (31.5%) | 3,861 (23.9%) |
| Number of persons who started the follow-up | 9603 (93.5%) | 32425 (95.8%) | 7274 (93.2%) | < 5 | 10696 (92.3%) | 6760 (91.3%) | 15388 (95.4%) |
| Total follow-up time regardless of interruptions from start of follow-up (PY) | 29,437 | 107,300 | 12,551 | 8 | 32,272 | 13,054 | 44,755 |
| Number of vaccinations during follow-up (median, IQR) | 3 | 0 | 0 | 4.5 | 2 | 0 | 3 |
| Number of people with vaccinations (n/%): 0 | 2,156 (21%) | 26,355 (77.9%) | 3,829 (49%) | 0 (0%) | 3,024 (26.1%) | 4,139 (55.9%) | 2,576 (16%) |
| Number of people with vaccinations (n/%): 1 | 894 (8.7%) | 2,700 (8%) | 1,335 (17.1%) | 0 (0%) | 852 (7.4%) | 917 (12.4%) | 1,271 (7.9%) |
| Number of people with vaccinations (n/%): 2 | 1,234 (12%) | 1,371 (4.1%) | 1,044 (13.4%) | 0 (0%) | 1,579 (13.6%) | 802 (10.8%) | 1,910 (11.8%) |
| Number of people with vaccinations (n/%): 3 or more | 5319 (51.8%) | 1999 (5.9%) | 1066 (13.7%) | < 5 | 5241 (45.2%) | 902 (12.2%) | 9631 (59.7%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

Table 79 presents the prevalence of comorbidities and comedication use of the UC study population during the look-back period. The prevalence of individuals with immunocompromised status ranged from 7.4% in BIFAP to 37.5% in NHR. Malignancy accounted for 3.9% to 6.3% across data sources. The prevalence of atopic dermatitis ranged from 0.1% (SNDS) to 2.5% (SIDIAP), whereas immunosuppressants ranged from

11.8% (BIFAP) to 33.4% (SNDS). Analgesics use was lower in CPRD (20.8%) and higher in SNDS (70.7%), while systemic corticosteroids accounted for 9.9% (BIFAP) to 29.7% (SNDS). Overall, SNDS reports the highest prevalence of drug use across most therapeutic groups, with some exceptions. Diabetes medications were higher in SIDIAP (10.8%) and lower in NHR (4.9%). Drugs to treat mental health diseases, lipid-lowering drugs and cardiovascular medication were higher in BIFAP, CPRD, VID and SIDIAP. Anti-epileptics were higher only in VID. No NSAIDs were found in SNDS, whereas accounted for 6.9% to 28.2% in the rest of the databases except for PEDIANET. Between 0.6% (CPRD) to 4.4% (SNDS) of UC patients had a dispensing or prescription of TNF inhibitors during the look-back period, with no cases in SIDIAP and PEDIANET.

*Table 79. Comorbidities and comedication in the UC study cohort.*

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | 10,273 | 33,833 | 7,808 | 2 | 11,584 | 7,403 | 16,132 |
| Immunocompromise status (n/%) | 762 (7.4%) | 5,261 (15.5%) | 1,455 (18.6%) | 0 (0%) | 1,117 (9.6%) | 912 (12.3%) | 6,048 (37.5%) |
| Malignancy (n/%) | 397 (3.9%) | 1,306 (3.9%) | 491 (6.3%) | 0 (0%) | 633 (5.5%) | 432 (5.8%) | 935 (5.8%) |
| Atopic dermatitis (n/%) | 204 (2%) | 485 (1.4%) | 44 (0.6%) | 0 (0%) | 285 (2.5%) | 5 (0.1%) | 336 (2.1%) |
| Immunosuppressants and Corticosteroids for systemic use (n/%) | 1,214 (11.8%) | 7,136 (21.1%) | 1,564 (20%) | 0 (0%) | 1,735 (15%) | 2,472 (33.4%) | 3,710 (23%) |
| Immunostimulants (n/%) | 0 (0%) | < 5 | 22 (0.3%) | 0 (0%) | 0 (0%) | 47 (0.6%) | 28 (0.2%) |
| Analgesics (n/%) | 3,687 (35.9%) | 7,042 (20.8%) | 3,805 (48.7%) | < 5 | 5,101 (44%) | 5,232 (70.7%) | 3,948 (24.5%) |
| Systemic corticosteroids (n/%) | 1,015 (9.9%) | 4,987 (14.7%) | 965 (12.4%) | 0 (0%) | 1,355 (11.7%) | 2,196 (29.7%) | 2,947 (18.3%) |
| Antithrombotic agents (n/%) | 1,549 (15.1%) | 3,801 (11.2%) | 1,138 (14.6%) | 0 (0%) | 2,137 (18.4%) | 1,369 (18.5%) | 2,140 (13.3%) |
| Sex hormones (n/%) | 319 (3.1%) | 3,996 (11.8%) | 229 (2.9%) | 0 (0%) | 303 (2.6%) | 1,057 (14.3%) | 0 (0%) |
| Diabetes medications (n/%) | 845 (8.2%) | 2407 (7.1%) | 694 (8.9%) | < 5 | 1248 (10.8%) | 499 (6.7%) | 789 (4.9%) |
| Antibiotics (n/%) | 2769 (27%) | 10906 (32.2%) | 3127 (40%) | < 5 | 3721 (32.1%) | 3928 (53.1%) | 4462 (27.7%) |
| Antiviral drugs (n/%) | 117 (1.1%) | 460 (1.4%) | 190 (2.4%) | 0 (0%) | 137 (1.2%) | 332 (4.5%) | 321 (2%) |
| Antimycotics (n/%) | 102 (1%) | 476 (1.4%) | 0 (0%) | 0 (0%) | 114 (1%) | 346 (4.7%) | 0 (0%) |
| Non-steroidal anti-inflammatory drugs (n/%) | 2,046 (19.9%) | 2,331 (6.9%) | 2,199 (28.2%) | < 5 | 2,501 (21.6%) | 0 (0%) | 3,275 (20.3%) |
| Drug to treat mental health diseases (n/%) | 1,633 (15.9%) | 7,323 (21.6%) | 1,366 (17.5%) | 0 (0%) | 2,376 (20.5%) | 1,016 (13.7%) | 1,783 (11.1%) |
| Lipid lowering drugs (n/%) | 1,790 (17.4%) | 5,941 (17.6%) | 1,601 (20.5%) | 0 (0%) | 2,312 (20%) | 1,154 (15.6%) | 2,192 (13.6%) |
| Cardiovascular medication (n/%) | 3,283 (32%) | 11,742 (34.7%) | 2,742 (35.1%) | 0 (0%) | 4,546 (39.2%) | 2,384 (32.2%) | 1,962 (12.2%) |
| Oncologic drugs (n/%) | 132 (1.3%) | 893 (2.6%) | 242 (3.1%) | 0 (0%) | 204 (1.8%) | 236 (3.2%) | 204 (1.3%) |
| Anti-epileptics (n/%) | 616 (6%) | 586 (1.7%) | 590 (7.6%) | 0 (0%) | 929 (8%) | 393 (5.3%) | 592 (3.7%) |
| Diuretics (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

| Covariates at baseline | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Tumor necrosis factor (TNF) inhibitor (n/%) | 0 (0%) | 210 (0.6%) | 231 (3%) | 0 (0%) | 0 (0%) | 324 (4.4%) | 403 (2.5%) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.10.3 IRs of UC flares

#### 10.10.3.1 IRs of UC flares in the general population

Variability was observed for the IR of the UC flare episodes across data sources. The number of individuals who developed a first UC flare episode in CPRD was 10,094 leading to an IR of 129.3 per 1,000 PY (CI 95% 126.7-131.8). In VID, 1,819 persons developed a first flare-up episode, leading to an IR of 202.7 per 1,000 PY (CI 95% 193.5-212.3). In SIDIAP, 3,852 patients developed a first flare-up episode accounting for an IR of 212.2 per 1,000 PY (CI 95% 205.5-219). In SNDS, 2,822 subjects flared-up, leading to an IR of first flare episode of 384.9 per 1,000 PY (CI 95% 370.9-399.4). Finally, in NHR, 4,228 patients developed a first flare, leading to an IR of 162.2 per 1,000 PY (CI 95% 157.4-167.2).

Overall, the IRs of the second flare episodes decreased in all data sources, except for a 44% increase in VID (363.9 per 1,000 PY) and almost equal values in CPRD (128.1 per 1,000 PY). The other data sources reported 176.3 cases in BIFAP, 158.5 cases in SIDIAP, 271.6 in SNDS, and 153.9 in NHR per 1,000 PY. On average, in those data sources, the IRs of the second flare episode decreased by around 5 to 29% compared to the first flare episode.

The IRs of the third flare-up episode increased in comparison to the second flare episodes IRs in all data sources. The observed IRs for the third episode are 187.9 in BIFAP, 183.7 in CPRD, 687.9 in VID, 209.7 in SIDIAP, 378.8 in SNDS, and 194.1 in NHR per 1,000 PY. On average, in those data sources, the IRs of the third flare episode increased by around 6% to 47% in comparison to the second flare episode (Table 80).

*Table 80. Background incidence rate of first, second, and third flare in the UC cohort, per 1,000 person-years, with 95% confidence intervals.*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Total cohort population | NA | NA | NA | NA | NA | NA | NA |
| Number of persons who started the follow-up | 9,491 | 32,292 | 7,196 | < 5 | 10,603 | 6,535 | 15,299 |
| Number of flares before entering follow-up | 4,887 | 6,134 | 1,679 | < 5 | 5,673 | 3,918 | 3,368 |
| Number of persons who develop a first flare-up episode | 3,462 | 10,094 | 1,819 | < 5 | 3,852 | 2,822 | 4,228 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 222.7 (215.3-230.2) | 129.3 (126.7-131.8) | 202.7 (193.5-212.3) | 9131.2 (1105.8-32985.2) | 212.2 (205.5-219) | 384.9 (370.9-399.4) | 162.2 (157.4-167.2) |
| Number of persons still in the study 90 days after first flare | 3,148 | 9,381 | 1,571 | < 5 | 3613 | 2446 | 3897 |
| Number of persons who develop a second flare-up episode | 871 | 2,336 | 408 | 0 | 853 | 688 | 848 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 176.3 (164.8-188.4) | 128.1 (123-133.4) | 363.9 (329.4-401) | 0 (0-654.4) | 158.5 (148-169.5) | 271.6 (251.7-292.7) | 153.9 (143.7-164.6) |

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|
| Number of persons still in the study 90 days after second flare | 755 | 2,122 | 315 | NA | 762 | 529 | 753 |
| Number of persons who develop a third flare-up episode | 187 | 572 | 96 | NA | 191 | 154 | 165 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 187.9 (162-216.9) | 183.7 (169-199.4) | 687.9 (557.2-840.1) | NA | 209.7 (181-241.7) | 378.8 (321.3-443.6) | 194.1 (165.6-226.1) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.10.3.2 IRs of UC flares stratified per age categories

Most of the people experiencing 1 to 3 episodes of UC flares were adults, especially 18-59 years old, followed by ≥ 60 years category and then 0–17-year-olds. PEDIANET observed very few 0-17 years old individuals developing a first flare episode (<5) and none for the subsequent ones. Overall, the incidence of flares showed slightly different patterns across age categories, data sources, and number of flare episodes. No clear patterns were observed: first flares were higher in 0-17-year-olds in 4 out of 6 data sources, and in 5 out of 6 data sources for second episodes, while third flares' rates were higher in ≥60-year-olds in 4 out of 6 data sources. For the 0-17-year-old category, the IRs per 1000 PY of the first flare ranged from 188.6 (BIFAP) to 649.7 (SNDS), the IRs of the second flare episodes span from 149.5 (VID) to 644.2 (SNDS) per 1000 PY, and the rates of the third flares were from 118.8 (CPRD) to 894.3 (SNDS). For this age category, from first to second flares, rates slightly decreased in all data sources except for BIFAP, where an increase was observed. From second to third flare, rates decreased in BIFAP, CPRD, and NHR while increasing in VID, SIDIAP, and SNDS. For the 18-59-year-old category, the IRs per 1000 PY of the first flare ranged from 121.1 (CPRD) to 393.9 (SNDS), for the second flare episodes span from 119.5 (CPRD) to 316.4 (VID), and for the third flare episodes span from 146.5 (CPRD) to 565.2 (VID). For this age category, from first to second flares, rates slightly decreased in all data sources except for VID, where an increase was observed. From the second to third flare, rates decreased only in BIFAP, while increasing in CPRD, VID, SIDIAP, SNDS and NHR. For the ≥ 60 years category, the IRs per 1000 PY of the first flare ranged from 135.5 (CPRD) to 341.9 (SNDS), for the second flare episodes span from 140.5 (CPRD) to 493.7 (VID), and for the third flare episodes span from 256.1 (CPRD) to 944.4 (VID). For this age category, from first to second flares, rates slightly decreased in all data sources except for CPRD and VID, where an increase was observed. From the second to third flare, a substantial increase was observed across all data sources.

*Table 81. Background incidence rate of first, second, and third flare in the UC cohort per 1,000 person-years (95% confidence interval) stratified per age categories (0-17, 18-59, and ≥60 years old).*

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 0-17 | 197 | 415 | 55 | < 5 | 148 | 129 | 242 |
| Number of persons who develop a first flare-up episode | 18-59 | 2073 | 5923 | 1095 | | 2119 | 1927 | 2980 |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | 60+ | 1192 | 3756 | 669 | | 1585 | 766 | 1006 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 188.6 (163.2-216.8) | 285.1 (258.3-313.9) | 189 (142.4-246) | 9131.2 (1105.8-32985.2) | 460.2 (389-540.6) | 649.7 (542.4-772) | 256.8 (225.4-291.2) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 219.1 (209.7-228.7) | 121.1 (118-124.2) | 183.1 (172.4-194.3) | NA | 192 (183.9-200.3) | 393.9 (376.5-411.9) | 158.1 (152.4-163.9) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | 60+ | 236.5 (223.2-250.3) | 135.5 (131.2-139.9) | 247.7 (229.3-267.3) | NA | 233.3 (222-245.1) | 341.9 (318.2-367) | 160.4 (150.7-170.7) |
| Number of persons still in the study 90 days after first flare | 0-17 | 177 | 371 | 46 | < 5 | 136 | 88 | 217 |
| Number of persons still in the study 90 days after first flare | 18-59 | 1961 | 5654 | 964 | | 2078 | 1720 | 2839 |
| Number of persons still in the study 90 days after first flare | 60+ | 1139 | 3730 | 589 | | 1542 | 702 | 1008 |
| Number of persons who develop a second flare-up episode | 0-17 | 40 | 83 | 7 | 0 | 37 | 35 | 45 |
| Number of persons who develop a second flare-up episode | 18-59 | 536 | 1,334 | 231 | NA | 447 | 497 | 617 |
| Number of persons who develop a second flare-up episode | 60+ | 295 | 919 | 170 | NA | 369 | 156 | 186 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 226.4 (161.8-308.3) | 156.7 (124.8-194.3) | 149.5 (60.1-308) | 0 (0-654.4) | 216 (152.1-297.8) | 644.2 (448.7-895.9) | 203.1 (148.2-271.8) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 163.2 (149.7-177.6) | 119.5 (113.2-126.1) | 316.4 (276.9-360) | NA | 136.4 (124-149.6) | 273.2 (249.7-298.3) | 151.5 (139.8-163.9) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | 60+ | 199.3 (177.2-223.4) | 140.5 (131.6-149.9) | 493.7 (422.2-573.7) | NA | 190.7 (171.8-211.2) | 236.6 (200.9-276.7) | 152.8 (131.6-176.4) |
| Number of persons still in the study 90 days after second flare | 0-17 | 39 | 76 | 6 | NA | 33 | 25 | 38 |
| Number of persons still in the study 90 days after second flare | 18-59 | 479 | 1,249 | 178 | NA | 435 | 385 | 564 |
| Number of persons still in the study 90 days after second flare | 60+ | 271 | 868 | 138 | NA | 322 | 128 | 174 |
| Number of persons who develop a third flare-up episode | 0-17 | 5 | 11 | < 5 | | 10 | 12 | 6 |

| Characteristics | Ageband | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a third flare-up episode | 18-59 | 104 | 284 | 52 | | 88 | 101 | 115 |
| Number of persons who develop a third flare-up episode | 60+ | 78 | 277 | 43 | | 93 | 41 | 44 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 0-17 | 121.8 (39.5-284.2) | 118.8 (59.3-212.5) | 499.7 (12.7-2783.9) | NA | 332.9 (159.6-612.1) | 894.3 (462.1-1562.2) | 168.4 (61.8-366.5) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 18-59 | 153.1 (125.1-185.5) | 146.5 (129.9-164.5) | 565.2 (422.1-741.1) | NA | 155 (124.3-191) | 319.6 (260.4-388.4) | 171.8 (141.8-206.2) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | 60+ | 284 (224.5-354.4) | 256.1 (226.8-288.1) | 944.4 (683.4-1272.1) | NA | 297.2 (239.9-364.1) | 531.4 (381.4-720.9) | 303.3 (220.4-407.2) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.10.3.3 IRs of UC flares stratified per gender

Across data sources, the number of females who developed a first, second, or third episode of UC flares and their incidence was overall slightly higher than that of males, except for the rates of second flares in SNDS (almost equal across gender groups) as shown in Table 82. The IRs per 1000 PY of first UC flares for females ranged from 134.8 (CPRD) to 432.4 (SNDS), while male rates moved from 124.1 (CPRD) to 343.4 (SNDS). The number of cases and the IRs per 1000 PY of second UC flares were overall lower than in the first episodes, except for the rates of VID, which were higher for second flare episodes both in males and females. Overall, the second UC flares ranged from 128.7 (CPRD) to 400.7 (VID) per 1000 PY in females, while male rates moved from 127.5 (CPRD) to 318.5 (VID) per 1000 PY. The number of cases and the IRs per 1000 PY of third UC flares were higher than the second episodes, except for third episode rates in males for BIFAP. Overall, the IRS per 1000 PY of third UC flares ranged from 201.1 (CPRD) to 726.5 (VID) in females, while male rates moved from 167.1 (CPRD) to 632 (VID).

*Table 82. Background incidence rate of first, second, and third flare in the UC cohort per 1,000 person-years (95% confidence interval) stratified per gender.*

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons who develop a first flare-up episode | F | 1755 | 5074 | 1014 | | 1953 | 1480 | 2115 |
| Number of persons who develop a first flare-up episode | M | 1707 | 5020 | 805 | < 5 | 1899 | 1342 | 2113 |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | F | 228.1 (217.6-239.1) | 134.8 (131.1-138.5) | 228.7 (214.9-243.3) | NA | 214.4 (205-224.2) | 432.4 (410.6-455) | 173.3 (166-180.8) |
| IR of first flare-up episode, per 1,000 PY (CI 95%) | M | 217.3 (207.1-227.8) | 124.1 (120.7-127.6) | 177.4 (165.3-190) | 9131.2 (1105.8-32985.2) | 209.9 (200.6-219.6) | 343.4 (325.3-362.3) | 152.5 (146-159.1) |
| Number of persons still in the study 90 days after first flare | F | 1597 | 4710 | 874 | | 1840 | 1290 | 1945 |

| Characteristics | Gender | BIFAP-ES | CPRD-UK | VID-ES | PEDIANET-IT | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|---|---|
| Number of persons still in the study 90 days after first flare | M | 1551 | 4671 | 697 | < 5 | 1773 | 1156 | 1952 |
| Number of persons who develop a second flare-up episode | F | 439 | 1,183 | 248 | NA | 437 | 360 | 431 |
| Number of persons who develop a second flare-up episode | M | 432 | 1,153 | 160 | 0 | 416 | 328 | 417 |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | F | 179.8 (163.4-197.5) | 128.7 (121.5-136.3) | 400.7 (352.4-453.8) | NA | 158.8 (144.2-174.4) | 267.2 (240.3-296.3) | 164.8 (149.6-181.1) |
| IR of second flare-up episode, per 1,000 PY (CI 95%) | M | 172.8 (156.9-189.9) | 127.5 (120.3-135.1) | 318.5 (271-371.8) | 0 (0-654.4) | 158.1 (143.3-174.1) | 276.6 (247.5-308.3) | 144 (130.5-158.5) |
| Number of persons still in the study 90 days after second flare | F | 382 | 1,076 | 187 | NA | 395 | 286 | 383 |
| Number of persons still in the study 90 days after second flare | M | 373 | 1,046 | 128 | NA | 367 | 243 | 370 |
| Number of persons who develop a third flare-up episode | F | 100 | 306 | 60 |  | 96 | 89 | 86 |
| Number of persons who develop a third flare-up episode | M | 87 | 266 | 36 |  | 95 | 65 | 79 |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | F | 207.6 (168.9-252.4) | 201.1 (179.2-225) | 726.5 (554.4-935.2) | NA | 202.9 (164.3-247.7) | 419.3 (336.7-516) | 215.3 (172.2-265.9) |
| IR of third flare-up episode, per 1,000 PY (CI 95%) | M | 169.5 (135.8-209.1) | 167.1 (147.6-188.5) | 632 (442.7-875) | NA | 217.2 (175.7-265.5) | 334.6 (258.2-426.5) | 175.3 (138.8-218.5) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

#### 10.10.3.4 IRs of UC flares in pregnant population

VID identified 93 pregnant women who have at least one pregnancy after the start of follow-up for the UC cohort population. The IR per 1,000 PY of the first flare episode of UC among pregnant population in VID was 627.7 (CI 95% 402.2-934) with 24 observed events. SIDAP identified 133 pregnant women who have at least one pregnancy after the start of follow-up for the UC cohort population. The IR per 1,000 PY of the first flare episode of UC among pregnant population in SIDAP was 201.2 (CI 95% 107.1-344) with 13 observed events. NHR identified 555 pregnant women who have at least one pregnancy after the start of follow-up for the UC cohort population. The IR per 1,000 PY of the first flare episode of UC among pregnant population in NHR was 214.9 (CI 95% 161.9-279.7) with 55 observed events. Across all data sources, the episodes of second and third flares did drop consistently, with <5 cases observed. BIFAP, CPRD, SNDS did not run the pregnancy algorithm. See Table 83 below.

*Table 83. Background IR in pregnant population of first, second, and third flare in the UC study cohort, per 1,000 person-years (95% confidence intervals).*

| Cohort characteristics | BIFAP-ES | CPRD-UK | VID-ES | SIDIAP-ES | SNDS-FR | NHR-NO |
|---|---|---|---|---|---|---|
| Number of persons who have at least one pregnancy after start of follow-up | NA | NA | 93 | 133 | NA | 555 |
| Number of persons who develop a first flare-up episode while they are pregnant | NA | NA | 24 | 13 | NA | 55 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 627.7 (402.2-934) | 201.2 (107.1-344) | NA | 214.9 (161.9-279.7) |
| Number of persons who have at least one pregnancy after the first flare | NA | NA | 15 | 34 | NA | 154 |
| Number of persons who develop a second flare-up episode while they are pregnant | NA | NA | < 5 | < 5 | NA | 17 |
| IR of first flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 453.4 (54.9-1638) | 64.1 (1.6-357.3) | NA | 266 (154.9-425.9) |
| Number of persons who have at least one pregnancy 90 days after second flare | NA | NA | < 5 | 5 | NA | 23 |
| Number of persons who develop a third flare-up episode while they are pregnant | NA | NA | 0 | < 5 | NA | < 5 |
| IR of third flare-up episode while pregnant, per 1,000 PY (CI 95%) | NA | NA | 0 (0-3246.7) | 503.1 (12.7-2803.1) | NA | 364.9 (75.2-1066.3) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

### 10.10.4 Six- and twelve-months cumulative incidence of flares of UC

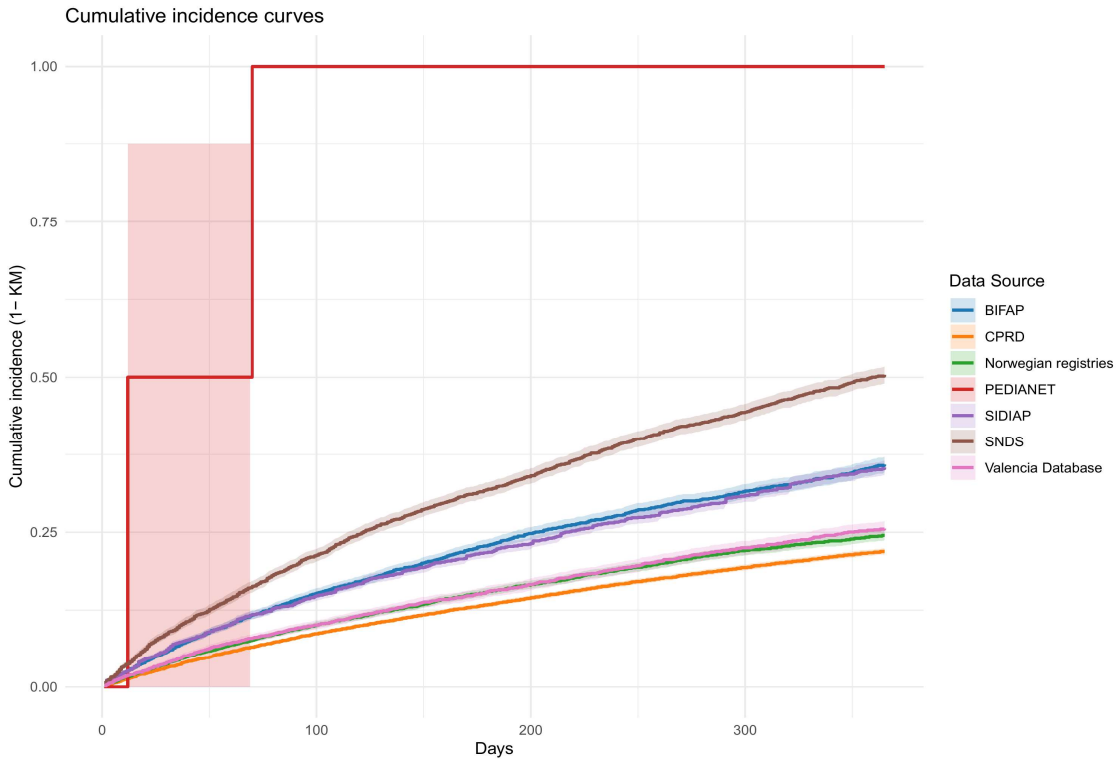
Table 84 shows the 6- and 12-months cumulative incidence of the first flare episode of UC. The 6-month risk of a first flare in UC patients was 15.5% in VID, 21.8% in SIDIAP, 22.9% in BIFAP, 31.9% for SNDS, 15.5% in NHR, and 13.4% in CPRD. The 12-month risk for a first flare was 25.6% in VID, 35.4% in SIDAP, 35.9% in BIFAP, 50.4% in SNDS, 24.5% in NHR, and 21.9% in CPRD. The cumulative incidence curve is represented in Figure 22.

*Table 84. Six- and twelve-months cumulative incidence of flares of UC (95% confidence interval)*

| Days | NHR-NO | VID-ES | SIDIAP-ES | BIFAP-ES | PEDIANET-IT | SNDS-FR | CPRD-UK |
|---|---|---|---|---|---|---|---|
| 180 | 0.155 (0.148-0.161) | 0.155 (0.146-0.164) | 0.218 (0.209-0.226) | 0.229 (0.219-0.239) | 1 (NA-NA) | 0.319 (0.307-0.33) | 0.134 (0.13-0.137) |
| 365 | 0.245 (0.237-0.253) | 0.256 (0.244-0.268) | 0.354 (0.342-0.365) | 0.359 (0.346-0.371) | 1 (NA-NA) | 0.504 (0.49-0.517) | 0.219 (0.214-0.224) |

NA = Data Not Available; NR = Data Available but Not Reportable (because this value can allow <5 cells calculations).

*Figure 22. Cumulative incidence curve UC.*



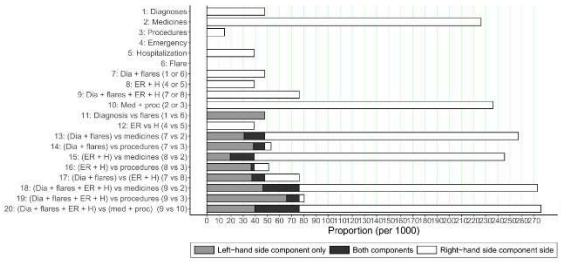

### 10.10.5 Other analyses

#### 10.10.5.1 Component analysis

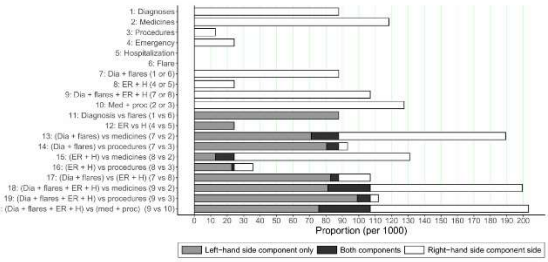
MED was the highest component of the 12-month cumulative incidence of the first UC flare episode in all data sources (see Figure 23), ranging from 58.2% (VID) to 82.1% (BIFAP). The remaining cases were mainly identified via DIA (NHR and CPRD), DIA and ER (VID), DIA and H (SNDS, SIDIAP and BIFAP). The overlapping across components (MED, DIA, ER, H) ranged from 6.6% (CPRD) to 19.7% (SNDS).

*Figure 23. Component Analysis for UC*

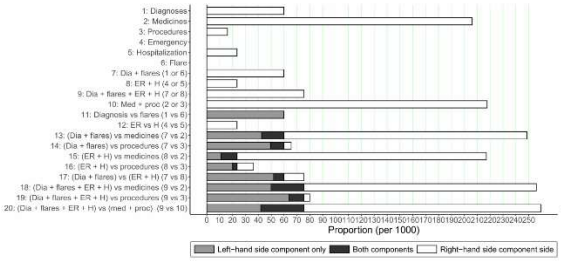
**BIFAP**



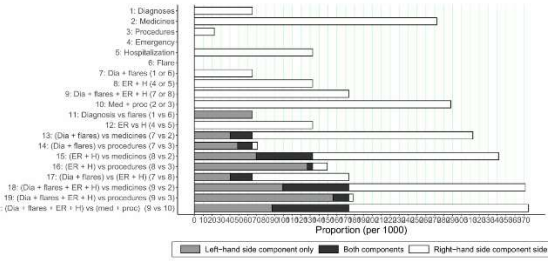

**VID**



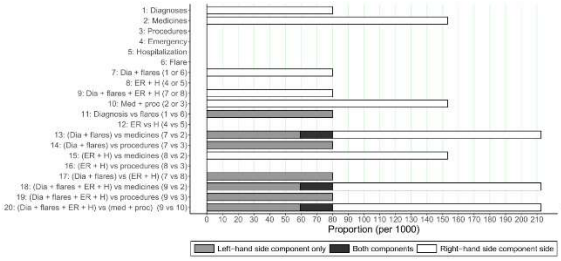

**SIDIAP**



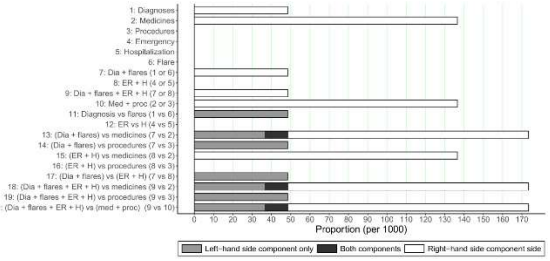

**SNDS**




**NHR**




**CPRD**



# 11 DISCUSSION

## 11.1 KEY RESULTS

This study aimed to describe the background incidence and 6- and 12-month risk of flares of 10 auto-immune diseases, selected based on their relevance, the limited RWD-based epidemiological evidence on their flares, and the potential impact that vaccination may have on these pre-existing conditions. Flare rates and risks were relatively high in all conditions, although they varied by data source and by disease. The rates of second and third flares decreased in general compared to the first flare episodes. Each of the auto-immune conditions were identified by diagnostic codes. In the creation of the HT, EN and MS study cohorts, additional exclusion criteria were applied with the aim of adding specificity to the identification of the condition ended up having a large impact on the number of retained individuals in each cohort. This highlights the fact that further improvement of the algorithm proposals could be applied, which could be fine-tuned by the performance of sensitivity analyses for assessing the impact of removing those specific exclusion criteria. Demographic distributions of the cohorts were aligned with prior knowledge about the diseases of interest, showing external validity of the data. Flaring rates in females were higher compared to males in 5 diseases (MS, SLE, RA, PsA, UC). The risk of developing a first flare at one-year was 30% to 50% in all diseases, expect in MS and SLE, where the risk increased to 60%.

Limited epidemiological evidence is available on the incidence of flares for the diseases selected for the purpose of this study. On one hand, this hampers external validation of our results. On the other hand, this highlights the importance of the findings, which set these results as potential epidemiological benchmarks for future pharmacoepidemiologic studies by offering the first background IRs of flare episodes in these pre-existing conditions which can be essential for contextualizing and monitoring vaccine safety signals, e.g. through observed-to-expected analysis, and assessing the risk of flares associated with vaccination. In fact, over the last two decades, several vaccines and their effects have been investigated regarding the development of flares of inflammatory-related diseases or their ability to trigger them, but causality has not been proved (5,7–12,58). Moreover, these conditions are generally underrepresented in clinical trials, and their flares are challenging to be evaluated during both pre- and post-authorisation.

This work also stands as an operational proposal for specific algorithms to identify flares associated with the pre-selected 10 auto-immune conditions, which are not available yet as far as we know. Our algorithms were developed cooperatively by merging key knowledge from pharmacoepidemiologists, medical doctors, pharmacists, and clinicians with expertise on the conditions of interest. While, in this work, we had to tailor the algorithms to the participating data sources' and common data model's characteristics, a wider and more general proposal for the algorithms is available in the clinical definition forms (**Annex 1**). These definitions stand as an initial guide to identify the selected diseases' flares in large electronic health records data sources, as well as a starting point for further implementation and discussions about the algorithms' criteria, or as a general methodological strategy that could be potentially extended to the development of phenotyping algorithms for other conditions and their flaring.

A tailored analysis of each flare identification algorithm was performed to understand the contribution of the different algorithm components to the reported IR. The component analysis showed that the most important component of the flare identification strategies across all conditions were medications (MED). For some diseases, like UC, SLE, EN and

PAN, the component analysis showed that diagnoses of disease of interest recorded in hospital discharge records (H) or emergency room (ER), or other diagnoses (DIA), that can be considered as proxy of flare also depending on the available information from each data source specifically extracted for the data instance, could still add a variable but non-negligible proportion of flare cases. Moreover, to reduce the risk of misclassification bias, H is considered as a component only if marked as main diagnosis. In VID, the main diagnosis associated to hospitalization was not labelled as such, thus, the H component was not usable for this data source. Therefore, the possibility of a slight underestimation should be taken in consideration in case such components of the identification strategy are not available, or specific data prompt are missing (e.g., DIA does not include diagnoses recorded during secondary care encounters). The component strategy also allowed to highlight possible issues in the component algorithm implementation to be further investigated. This was the case of GD or HT, where the extreme inter-data source variability of results from the same components could not be explained by data source characteristics and underlying data prompt only.

## 11.2 LIMITATIONS

First, this study uses available data sources, which capture different type of data and information. Not all data sources capture the same type of information which could impact on the ability to identify chronic diseases and their flares. However, since most of the flares were identified based on medications, differences in use and reimbursement policies, may have impacted flare rates, as well as use for other indications. For instance, a main limitation for some of the participating data sources was the lack of specific information, e.g. the SNDS claims database lacks diagnosis information and only allows the identification of events requiring hospitalisation. Consequently, the actual estimated incidences are probably underestimated by taking into account only the more severe cases. Moreover, SNDS did not include NSAIDs and diuretics in the data instance used in this study, therefore prevalence of use of these therapeutic groups during the lookback were not reported.

Second, although changes in the doses of the recommended drugs to treat the selected diseases might be useful information to identify potential flare episodes, posology information was not possible to be captured from the available data instances as this information was not converted to the Common Data Model (CDM). This may impact the identification of flares leading to some misclassification. Finally, our operational phenotype algorithms are defined based on agreed clinical definitions across different complementary expertise. Although these phenotype algorithms have been developed by a team of epidemiologists and clinical experts, they have not been formally tested.

Identification of all conditions was based on diagnostic codes only and not confirmed with laboratory tests (when important for the condition) due to unavailability of these results in the participating data sources. This may have resulted in an overestimation of the size and nature of the cohorts, including false positive cases, and a subsequent underestimation of flares, if these persons did not have the condition of interest.

## 11.3 INTERPRETATION

We selected 10 auto-immune diseases of interest and calculated background incidence rates and the 6- and 12-months risks to develop a first flare. Most of the flares were identified through medicines use. Application of additional exclusion criteria in HT, EN and MS cohorts with the scope of adding specificity to the identification of the condition

had a large impact on the number of retained individuals in each cohort and could be further investigated through sensitivity analyses to facilitate fine-tuning of the herein proposed definitions. Rates of flares were high, and since the medications may also have been prescribed for other conditions, this may lead to some overestimation. The data sources captured different type of information, and this may have impacted the ability to identify chronic diseases and their flares. This is particularly evident for the Italian PEDIANET data source, which only contains information about paediatric populations. There is very little information on the incidence or risk of flares in the literature. Overall, this is an exploratory work.

## 11.4 GENERALISABILITY

This study comprises data sources from multiple European countries, the cohorts of newly diagnosed 10 auto-immune diseases had age and gender patterns consistent with prior publication on these diseases, as specified for each disease in the corresponding result section, where appropriated.

# 12 OTHER INFORMATION

**LIST of ANNEXES:**

- Annex 1: Clinical Definition Forms.

# 13 CONCLUSIONS

This study aimed to describe background incidence rates and 6- and 12-month risk of flares for 10 selected auto-immune diseases. Flare rates are relatively high in all conditions, although they varied across data sources. Flare rates of second and third flares in those with a prior rate, decreased in general. Flare events are mostly identified through medication use (start of a new drug), which may introduce some overestimation due to the use of the selected drugs in other indications and the absence of posology information.

# 14 REFERENCES


1. Salmon DA, Lambert PH, Nohynek HM, Gee J, Parashar UD, Tate JE, et al. Novel vaccine safety issues and areas that would benefit from further research. BMJ Glob Health. mayo de 2021;6(Suppl 2):e003814.

2. Ricotta EE, Rid A, Cohen IG, Evans NG. Observational studies must be reformed before the next pandemic. Nat Med 2023 298. junio de 2023;29(8):1903-5.

3. Vaccine Monitoring Platform | European Medicines Agency [Internet]. Disponible en: https://www.ema.europa.eu/en/about-us/what-we-do/crisis-preparedness-management/vaccine-monitoring-platform

4. Xie Y, Liu Y, Liu Y. The Flare of Rheumatic Disease After SARS-CoV-2 Vaccination: A Review. Front Immunol. julio de 2022;13:919979.

5. Paik JJ, Sparks JA, Kim AHJ. Immunogenicity, breakthrough infection, and underlying disease flare after SARS-CoV-2 vaccination among individuals with systemic autoimmune rheumatic diseases. Curr Opin Pharmacol. agosto de 2022;65:102243.

6. Lenfant T, Jin Y, Kirchner E, Hajj-Ali RA, Calabrese LH, Calabrese C. Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients. Rheumatology. noviembre de 2021;60(11):5149-57.

7. Carubbi F, Alunno A, Santilli J, Natali L, Mancini B, Gregorio ND, et al. Immune-mediated inflammatory diseases after anti-SARS-CoV-2 vaccines: new diagnoses and disease flares. RMD Open. 1 de septiembre de 2022;8(2):e002460.

8. Grimaldi L, Papeix C, Hamon Y, Buchard A, Moride Y, Benichou J, et al. Vaccines and the Risk of Hospitalization for Multiple Sclerosis Flare-Ups. JAMA Neurol. 1 de octubre de 2023;80(10):1098-104.

9. Li X, Tong X, Yeung WWY, Kuan P, Yum SHH, Chui CSL, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis. 1 de abril de 2022;81(4):564-8.

10. Farisogullari B, Lawson-Tovey S, Hyrich KL, Gossec L, Carmona L, Strangfeld A, et al. Factors associated with disease flare following SARS-CoV-2 vaccination in people with inflammatory rheumatic and musculoskeletal diseases: results from the physician-reported EULAR Coronavirus Vaccine (COVAX) Registry. Ann Rheum Dis. 1 de noviembre de 2024;83(11):1584-95.

11. Geldof J, Truyens M, Sabino J, Ferrante M, Lambert J, Lapeere H, et al. SARS-CoV-2 infection and COVID19 vaccination across eight immune-mediated inflammatory disorders: A prospective, real-life Belgian cohort study – the BELCOMID study. Front Immunol [Internet]. 1 de marzo de 2023 [citado 24 de febrero de 2025];14. Disponible en: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1126351/full

12. Stefanizzi P, Moscara L, Palmieri C, Martinelli A, Di Lorenzo A, Venerito V, et al. Safety profile of recombinant adjuvanted anti-herpes zoster vaccine (RZV) in high-risk groups: Data from active surveillance program. Puglia (Italy), 2021–23. Vaccine. 30 de abril de 2024;42(12):2966-74.

13. Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age. Vaccine. 2 de septiembre de 2011;29(38):6592-7.

14. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf. 2016;25(2):215-22.

15. Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. The Lancet. 19 de diciembre de 2009;374(9707):2115-22.

16. Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang WT, et al. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety. Vaccine. mayo de 2021;39(19):2712-8.

17. Willame C, Dodd C, Durán CE, Elbers RJHJ, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. enero de 2023;41(1):251-62.

18. Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, et al. Quantifying outcome misclassification in multi-database studies: The case study of pertussis in the ADVANCE project. Vaccine. diciembre de 2020;38 Suppl 2:B56-64.

19. Durán CE, Gini R, Davide M, Riefolo F, Riera J, Hoxhaj V, et al. SAFETY-VAC: Network of Data Sources for Vaccine Safety Evaluation [Internet]. Zenodo; 2024 ago [citado 15 de febrero de 2025]. Disponible en: https://zenodo.org/records/13384860

20. SAFETY-VAC: Background incidence estimation of flares of pre-existing chronic diseases using pan-European electronic healthcare data sources. (SAFETY VAC) | HMA-EMA Catalogues of real-world data sources and studies [Internet]. [citado 24 de febrero de 2025]. Disponible en: https://catalogues.ema.europa.eu/node/4134/administrative-details

21. Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther. enero de 2022;111(1):321-31.

22. Graves' hyperthyroidism in nonpregnant adults: Overview of treatment - UpToDate [Internet]. Disponible en: https://www.uptodate.com/contents/graves-hyperthyroidism-in-nonpregnant-adults-overview-of-treatment

23. Wolff L, Horisberger A, Moi L, Karampetsou MP, Comte D. Polyarteritis Nodosa: Old Disease, New Etiologies. Int J Mol Sci 2023 Vol 24 Page 16668. noviembre de 2023;24(23):16668.

24. Chen M, Suzuki A, Thakkar S, Yu K, Hu C, Tong W. DILIrank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. Drug Discov Today. abril de 2016;21(4):648-53.

25. Matteo AD, Bathon JM, Emery P. Rheumatoid arthritis. The Lancet. noviembre de 2023;402(10416):2019-33.

26. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. enero de 2023;82(1):3-18.

27. Bingham CO, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, et al. Developing a Standardized Definition for Disease "Flare" in Rheumatoid Arthritis (OMERACT 9 Special Interest Group). J Rheumatol. octubre de 2009;36(10):2335-41.

28. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. febrero de 2018;17(2):162-73.

29. Treatment of acute exacerbations of multiple sclerosis in adults - UpToDate [Internet]. Disponible en: https://www.uptodate.com/contents/treatment-of-acute-exacerbations-of-multiple-sclerosis-in-adults

30. Pérez-Garza DM, Chavez-Alvarez S, Ocampo-Candiani J, Gomez-Flores M. Erythema Nodosum: A Practical Approach and Diagnostic Algorithm. Am J Clin Dermatol. mayo de 2021;22(3):367-78.

31. Royo AC, Elbers R, Weibel D, Hoxhaj V, Kurkcuoglu Z, Sturkenboom MC, et al. Real-World Evidence BRIDGE: a tool to connect protocol with code programming. medRxiv. mayo de 2024;2024.05.08.24306833.

32. Gini R, Pajouheshnia R, Gardarsdottir H, Bennett D, Li L, Gulea C, et al. Describing diversity of real world data sources in pharmacoepidemiologic studies: The DIVERSE scoping review. Pharmacoepidemiol Drug Saf. mayo de 2024;33(5):e5787.

33. Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther. enero de 2022;111(1):321-31.

34. Hoxhaj V, Navarro CLA, Riera-Arnau J, Elbers RJ, Alsina E, Dodd C, et al. INSIGHT: A Tool for Fit-for-Purpose Evaluation and Quality Assessment of Observational Data Sources for Real World Evidence on Medicine and Vaccine Safety. medRxiv. octubre de 2023;2023.10.30.23297753.

35. Hahn JW, Yang HR, Moon JS, Chang JY, Lee K, Kim GA, et al. Global incidence and prevalence of autoimmune hepatitis, 1970–2022: a systematic review and meta-analysis. eClinicalMedicine. noviembre de 2023;65:102280.

36. McWilliams DF, Rahman S, James RJE, Ferguson E, Kiely PDW, Young A, et al. Disease activity flares and pain flares in an early rheumatoid arthritis inception cohort; characteristics, antecedents and sequelae. BMC Rheumatol. 18 de noviembre de 2019;3(1):49.

37. Cribier B, Caille A, Heid E, Grosshans E. Erythema nodosum and associated diseases. A study of 129 cases. Int J Dermatol. 1998;37(9):667-72.

38. Blake T, Manahan M, Rodins K. Erythema Nodosum – A Review of an Uncommon Panniculitis. Dermatol Online J [Internet]. 2014 [citado 15 de febrero de 2025];20(4). Disponible en: https://escholarship.org/uc/item/2dt0z3mz

39. Chaker L, Cooper DS, Walsh JP, Peeters RP. Hyperthyroidism. The Lancet. febrero de 2024;403(10428):768-80.

40. Hyperthyroidism - The Lancet [Internet]. [citado 15 de febrero de 2025]. Disponible en: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02016-0/abstract

41. Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, et al. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmun Rev. 1 de octubre de 2020;19(10):102649.

42. Diaz A, Lipman Diaz EG. Hypothyroidism. Pediatr Rev. 1 de agosto de 2014;35(8):336-49.

43. Harbo HF, Gold R, Tintoré M. Sex and gender issues in multiple sclerosis. Ther Adv Neurol Disord. julio de 2013;6(4):237-48.

44. Ascherio A, Munger K. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention—An Update. Semin Neurol. 26 de abril de 2016;36(02):103-14.

45. Coyle PK. What Can We Learn from Sex Differences in MS? J Pers Med. octubre de 2021;11(10):1006.

46. Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. Ann Rheum Dis. marzo de 2023;82(3):351-6.

47. Du M, Dernie F, Català M, Delmestri A, Man WY, Brash JT, et al. Treatment of systemic lupus erythematosus: Analysis of treatment patterns in adult and paediatric patients across four European countries. Eur J Intern Med. agosto de 2024;S0953620524003443.

48. Cornet A, Andersen J, Myllys K, Edwards A, Arnaud L. Living with systemic lupus erythematosus in 2020: a European patient survey. Lupus Sci Med. abril de 2021;8(1):e000469.

49. Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. Ann Rheum Dis. 1 de marzo de 2023;82(3):351-6.

50. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. marzo de 2011;63(3):633-9.

51. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis. noviembre de 2019;78(11):1463-71.

52. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: A Nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res. junio de 2013;65(6):870-8.

53. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. [citado 24 de febrero de 2025]; Disponible en: https://onlinelibrary.wiley.com/doi/10.1002/art.30155

54. Lubrano E, Scriffignano S, Fatica M, Triggianese P, Conigliaro P, Perrotta FM, et al. Psoriatic Arthritis in Males and Females: Differences and Similarities. Rheumatol Ther. 1 de junio de 2023;10(3):589-99.

55. Navab R, Yeragudi Jangamareddy VR, Midthala NV, Kamalakannan T. A Young Female Case of Polyarteritis Nodosa Presenting With Multisystem Involvement and Acute Abdomen: A Case Report. Cureus [Internet]. 28 de diciembre de 2021 [citado 15 de octubre de 2024]; Disponible en: https://www.cureus.com/articles/79127-a-young-female-case-of-polyarteritis-nodosa-presenting-with-multisystem-involvement-and-acute-abdomen-a-case-report

56. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. enero de 2022;18(1):22-34.

57. Shah SC, Khalili H, Gower-Rousseau C, Olen O, Benchimol EI, Lynge E, et al. Sex-Based Differences in Incidence of Inflammatory Bowel Diseases—Pooled Analysis of Population-Based Studies From Western Countries. Gastroenterology. octubre de 2018;155(4):1079-1089.e3.

58. Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, et al. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15–59 years of age. Vaccine. 2 de septiembre de 2011;29(38):6592-7.