6 July 2022

Population incidence rates of pemphigoid in six European countries

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1. Rationale and background

Pemphigoid is autoantibody-mediated blistering skin diseases, in which the basal keratinocytes lose adhesion to the basement membrane. The major type of pemphigoid is bullous pemphigoid (BP).

BP is characterized by diffuse truncal and limb tense blisters, urticarial plaques, intense pruritus and sparing of mucosal membranes. The pathogenesis of BP depends on the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors. Several trigger factors, such as drugs (e.g. furosemide, heparin, ibuprofen, captopril) or thermal or electrical burns, surgical procedures, trauma, ultraviolet irradiation, radiotherapy, chemical preparations, transplants and infections may induce or exacerbate BP. The presence of diabetes, stroke, Parkinson's disease, and dementia can be associated with BP compared to the general population.

The incidence of BP has increased over the past decades as a result of population aging with multiple comorbidities and exposure to drugs that may potentially trigger the disease, as well as improvement in the clinical diagnosis. Epidemiological studies of BP in Europe demonstrate the incidence ranges from 2.5 to 42.8 cases/million/year. The frequency of BP also increases in patients older than 80 years, with nearly 150-330 new cases/million/year. Patients with BP have increased mortality, ranging from 10% to 40% in the first year.

Pemphigoid is sometimes discussed as a potential adverse drug reaction (ADR) after treatment with some drugs. Recently, it has been associated with some direct oral anticoagulant (DOAC) and some COVID-19 vaccines. To address such safety signals for COVID-19 vaccine and to be prepared for future regulatory discussions on signals focused on pemphigoid, population incidence rates for pemphigoid were calculated across six European databases: IQVIA™ Disease Analyser France, IQVIA™ Disease Analyser Germany, IQVIA™ Medical Research Data (IMRD UK), THIN® Spain, THIN® - Italy, THIN® - Romania.

2. Research question and objectives

The objective of this study was to address the following research questions:

- What is the incidence rate of pemphigoid stratified by age, sex and year of diagnosis?

- What is the incidence of pemphigoid stratified by season of diagnosis (Autumn, Winter, Spring, Summer)?

3. Research methods

3.1. Study design

This was a cohort study describing incidence rates (IRs).

3.2. Setting and study population

We estimated general and stratified IRs for pemphigoid in six EU databases which cover primary health care users from France, Germany, UK, Spain, Italy and Romania.

3.3. Variables

Outcomes

To define pemphigoid, we used database specific codes mapping to ICD10: L12 as follows:

> L12.0 Bullous pemphigoid
>
> L12.1 Cicatricial pemphigoid
>
> L12.2 Chronic bullous disease of childhood
>
> L12.3 Acquired epidermolysis bullosa
>
> L12.8 Other pemphigoid
>
> L12.9 Pemphigoid, unspecified

Specific codes used for each database are shown in Annex 2.

Population strata

- Age at midpoint of time period of interest (<20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80 year)
- Biological sex
- Quarter (season of diagnosis):   Q1-Winter 01-Jan to 31-March

          Q2-Spring 01-Apr to 30-Jun

          Q3-Summer 01-Jul to 30-Sep

          Q4-Autumn 01-Oct to 31-Dec

3.4. Data sources

The following databases were used: IQVIA™ Disease Analyser France, IQVIA™ Disease Analyser Germany, IMRD (UK), THIN® Spain, THIN® Italy, THIN® Romania. Brief descriptions are provided in Annex 1.

3.5. Statistical analysis

3.5.1. Main statistical methods

This study described the incidence of new onset pemphigoid diagnoses in patients contributing patient time to the databases listed above. Patients were required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients were excluded from the analysis if they had any prior history of the condition in the database.

The study period was from 2015 to 2019. Population incidence rates from 2020 and 2021 (or the most recent data available) were included for interest only as the "true" background rates might be distorted by a change in the way in which patients interacted with healthcare services during the COVID-19 pandemic.

Numerator

The numerator consisted of the number of patients who experienced the event of interest during the yearly or quarterly time period. Patients with any recorded baseline history of pemphigoid were excluded and patients were only able to contribute one event each.

Denominator

As with the numerators, patients with a baseline history of pemphigoid at the start of each quarter or year were excluded. Patient follow-up time was truncated at the occurrence of the first event after which they did not contribute to the analysis.

Analysis

Follow-up time was calculated using the following formula:

follow up time (years) = (end date for the period – start date for the period + 1) / 365.25

Time was truncated where patients entered or left the study cohort part way through a time period or where they had an event. The incidence rate was then calculated as the number of events divided by the total follow up time:

incidence rate = (number of new onset events) / (total follow up time (years))

This is presented as the number of events per 100,000 person-years and was calculated for the entire population as well as stratified by year, season (quarter), gender and age. Confidence intervals around incidence rates were calculated using exact method.

Analyses were performed by the EMA researchers, using the IHD platform for IQVIA™ Disease Analyser France and Germany and using SAS for IMRD, THIN® Spain, THIN® Italy and THIN® Romania.

3.5.2. Sensitivity analysis

Sensitivity analyses were not conducted.

3.6. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018). Standard operating procedures and internal process guidance were adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results. All documents and results of statistical analysis were reviewed by an experienced reviewer. The quality control of the data is the responsibility of the data holder.

3.7. Protection of human subjects

Patient confidentiality is protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals. For information entering the public domain such as publication in EU PAS register, and in accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database and <10 in IQVIA™ Disease Analyzer France, THIN® Spain, Italy and Romania) were removed prior to publication of this report. Additional cells may have been redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

4. Results

4.1. Descriptive data

Table 1 shows the number of events, cumulative years of follow-up and incidence rates for each data sources.

Table 1. Number of new diagnoses of pemphigoid, cumulative years of follow-up and event rates for each data source (2015-2019)

data source	events	follow-up time (person years)	Rate per 100,000 (95% CI)
THIN® Italy	44	2,337,888	1.88 (1.37-2.53)
THIN® Romania	46	2,502,908	1.84 (1.35-2.45)
THIN® Spain	371	4,424,659	8.38 (7.55-9.28)
IMRD (UK)	447	8,210,212	5.44 (4.95-5.97)
IQVIA™ Disease analyzer – France	65	2,502,186	2.60 (2.04 - 3.31)
IQVIA™ Disease analyzer – Germany	883	12,664,625	6.97 (6.53 - 7.45)

4.2. Main results

The full results for each data source are shown in Annex 3 and stratified incidence rates are summarised in Table 2.

In general incidence rates increased with age for both sexes across all database, although the extent of this trend varied with Romania not showing a big difference, whilst Spain and UK were more pronounced. There was little difference in event rates between males and females. The most notable differences were for IQVIA™ Disease Analyser Germany where rates were higher for males *vs* female (8.06 *vs* 5.76 per 100,000 person years) and for THIN® Italy where IRs where lower for males than females (1.29 *vs* 2.40 per 100,000 person years).

Generally, IRs were higher in Q3 (summer) than at other times. There are no literature values describing a seasonal variation in pemphigoid incidence although sunlight is reported as being a trigger factor.

Change in the incidence rate with time are shown in Figure 1. Between 2015 and 2019, there was no clear consistent trend with time. In 2020 and 2021, most databases showed an increased IRs; however, this change can be attributed to a change in health seeking behaviour during the Covid-19 pandemic, which can differentially affect both the numerators and denominators. Also, in databases where patient observability ends at the last patient visit, the size of the denominator shrinks towards database end (e.g., last year) whereas the numerator is unchanged, which results in artificially increased incidence rates towards database end. For these reasons, the main results exclude data from these two years.
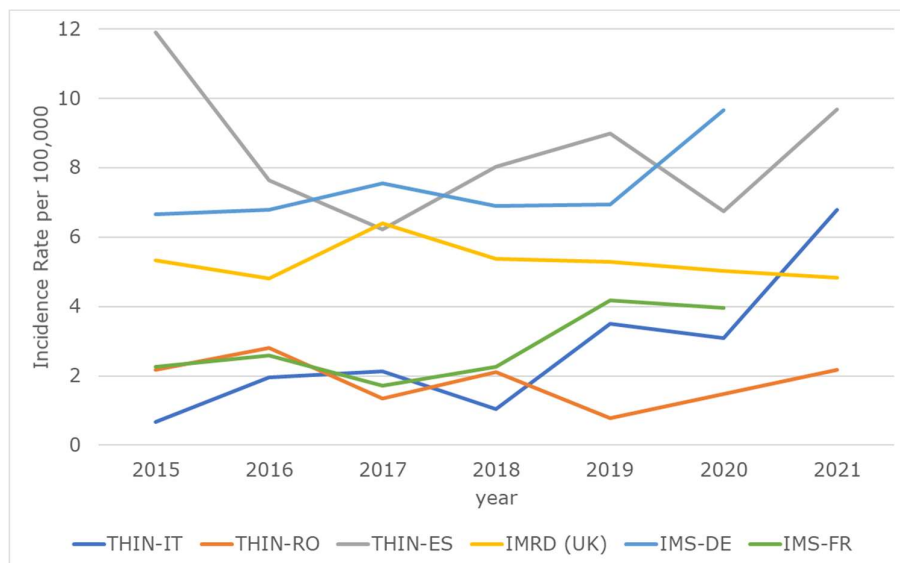
Figure 1. Incidence rate of pemphigoid by year and data source[1]

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[1] THIN-IT = THIN® Italy, THIN-RO = THIN® Romania, THIN-ES = THIN® Spain, IMS-DE = IQVIA™ Disease Analyser Germany, IMS-FR = IQVIA™ Disease Analyser France

Table 2. Summary of pemphigoid incidence rates (IR) for each data source (rates per 100,000 person years)

	THIN® Italy IR (95% C)	THIN® Romania IR (95% C)	THIN® Spain IR (95% C)	IMRD (UK) IR (95% C)	IQVIA™ Disease Analyser Germany IR (95% C)	IQVIA™ Disease Analyser France IR (95% C)
overall	1.88 (1.37-2.53)	1.84 (1.35-2.45)	8.38 (7.55-9.28)	5.44 (4.95-5.97)	6.97 (6.53-7.45)	2.60 (2.04-3.31)
2015	0.67 (0.14-1.95)	2.18 (1.04-4.00)	12.0 (9.49-14.9)	5.33 (4.23-6.62)	6.66 (5.70-7.78)	2.26 (1.24-4.15)
2016	1.96 (0.90-3.72)	2.81 (1.53-4.71)	7.63 (5.90-9.71)	4.80 (3.78-6.00)	6.78 (5.83-7.89)	2.58 (1.52-4.42)
2017	2.14 (1.03-3.93)	1.35 (0.54-2.78)	6.23 (4.73-8.05)	6.40 (5.24-7.74)	7.55 (6.56-8.69)	1.71 (0.91-3.25)
2018	1.05 (0.34-2.44)	2.11 (1.05-3.78)	8.04 (6.36-10.0)	5.38 (4.34-6.60)	6.90 (5.98-7.97)	2.27 (1.31-3.96)
2019	3.51 (2.04-5.62)	0.79 (0.22-2.03)	8.99 (7.22-11.1)	5.29 (4.26-6.48)	6.95 (6.01-8.05)	4.18 (2.74-6.39)
2020*	3.10 (1.73-5.11)	1.49 (0.60-3.07)	6.75 (5.23-8.57)	5.03 (4.04-6.18)	9.66 (8.45-11.1)	3.96 (2.45-6.44)
2021*	6.80 (4.55-9.76)	2.18 (0.94-4.30)	9.68 (7.44-12.4)	4.84 (3.88-5.96)		
<20years	0.00 (0.00-2.45)	1.46 (0.67-2.78)	2.04 (1.21-3.22)	0.21 (0.06-0.54)	2.05 (1.32-3.19)	0.00 (0.00-0.63)
20-29years	0.00 (0.00-1.55)	1.00 (0.12-3.62)	2.18 (1.04-4.01)	0.88 (0.40-1.67)	0.93 (0.55-1.59)	0.38 (0.09-2.09)
30-39years	0.00 (0.00-1.30)	0.77 (0.09-2.80)	2.11 (1.15-3.54)	0.66 (0.28-1.30)	1.02 (0.63-1.65)	0.97 (0.35-2.85)
40-49years	0.48 (0.06-1.75)	0.30 (0.01-1.70)	1.76 (0.94-3.01)	1.21 (0.66-2.02)	1.28 (0.85-1.91)	0.29 (0.07-1.60)
50-59years	0.71 (0.15-2.07)	1.27 (0.35-3.25)	4.20 (2.74-6.15)	2.09 (1.33-3.14)	2.85 (2.25-3.61)	2.64 (1.41-5.01)
60-69years	1.70 (0.62-3.70)	3.06 (1.58-5.35)	9.30 (6.78-12.4)	7.05 (5.35-9.12)	6.89 (5.82-8.18)	2.64 (1.36-5.20)
70-79years	3.82 (1.91-6.83)	3.89 (1.86-7.15)	25.6 (20.6-31.6)	19.6 (16.2-23.5)	13.4 (11.7-15.3)	5.77 (3.33-10.1)
≥80years	11.7 (7.33-17.7)	4.40 (1.62-9.58)	67.2 (57.1-78.5)	54.6 (47.5-62.4)	37.0 (33.5-40.8)	21.5 (15.2-30.5)
male	1.29 (0.70-2.16)	1.89 (1.17-2.89)	8.70 (7.49-10.1)	5.33 (4.65-6.08)	8.06 (7.40-8.77)	2.42 (1.72-3.41)
female	2.40 (1.62-3.42)	1.79 (1.16-2.65)	8.09 (6.97-9.34)	5.56 (4.86-6.33)	5.76 (5.19-6.41)	2.80 (2.00-3.93)
male < 20years	0.00 (0.00-4.80)	1.28 (0.35-3.27)	1.11 (0.36-2.58)	0.20 (0.02-0.74)	2.63 (1.52-4.60)	0.00 (0.00-1.32)
male 20-29years	0.00 (0.00-3.18)	0.00 (0.00-4.21)	1.84 (0.50-4.71)	0.59 (0.12-1.73)	1.14 (0.59-2.24)	0.00 (0.00-2.52)
male 30-39years	0.00 (0.00-2.81)	0.93 (0.02-5.21)	2.58 (1.11-5.08)	0.33 (0.04-1.19)	1.11 (0.59-2.10)	1.74 (0.63-5.08)
male 40-49years	0.52 (0.01-2.87)	0.00 (0.00-2.54)	1.93 (0.78-3.97)	1.00 (0.37-2.17)	1.92 (1.22-3.03)	0.00 (0.00-2.00)
male 50-59years	0.50 (0.01-2.76)	0.71 (0.02-3.95)	4.02 (2.08-7.03)	1.24 (0.50-2.56)	3.51 (2.61-4.72)	2.25 (0.91-5.75)
male 60-69years	0.60 (0.02-3.34)	5.39 (2.47-10.24)	12.60 (8.44-18.1)	7.59 (5.16-10.8)	7.19 (5.72-9.06)	2.49 (1.01-6.38)
male 70-79years	3.84 (1.25-8.97)	3.99 (1.09-10.20)	31.70 (23.5-41.8)	21.0 (16.1-27.1)	13.5 (11.3-16.2)	3.57 (1.45-9.13)
male ≥80 years	8.58 (3.15-18.67)	4.22 (0.51-15.26)	81.0 (63.0-102)	68.6 (56.3-83.0)	38.3 (33.9-43.3)	19.2 (12.1-30.8)
female <20years	0.00 (0.00-4.99)	1.65 (0.54-3.86)	3.02 (1.61-5.16)	0.22 (0.03-0.79)	1.48 (0.73-3.05)	0.00 (0.00-1.22)
female 20-29years	0.00 (0.00-3.05)	1.79 (0.22-6.46)	2.48 (0.91-5.41)	1.16 (0.42-2.52)	0.72 (0.32-1.69)	0.83 (0.20-4.65)
female 30-39years	0.00 (0.00-2.43)	0.66 (0.02-3.69)	1.70 (0.62-3.70)	0.99 (0.36-2.15)	0.92 (0.45-1.90)	0.00 (0.00-2.72)
female 40-49years	0.46 (0.01-2.54)	0.55 (0.01-3.04)	1.59 (0.59-3.47)	1.43 (0.62-2.82)	0.58 (0.25-1.35)	0.61 (0.15-3.42)
female 50-59years	0.90 (0.11-3.25)	1.72 (0.35-5.02)	4.36 (2.38-7.32)	2.99 (1.71-4.86)	2.16 (1.47-3.18)	3.07 (1.35-7.16)
female 60-69years	2.69 (0.87-6.27)	1.33 (0.27-3.89)	6.30 (3.60-10.2)	6.52 (4.30-9.49)	6.56 (5.11-8.45)	2.80 (1.14-7.18)

	THIN® Italy IR (95% C)	THIN® Romania IR (95% C)	THIN® Spain IR (95% C)	IMRD (UK) IR (95% C)	IQVIA™ Disease Analyser Germany IR (95% C)	IQVIA™ Disease Analyser France IR (95% C)
female 70-79years	3.80 (1.39-8.27)	3.83 (1.40-8.33)	20.5 (14.5-28.1)	18.3 (13.9-23.7)	13.3 (10.8-16.2)	8.36 (4.30-16.5)
female ≥80 years	13.53 (7.74-22.0)	4.50 (1.23-11.5)	59.2 (47.5-72.9)	45.1 (36.9-54.5)	34.8 (29.5-41.0)	25.0 (15.0-41.9)
Q1-Winter	1.57 (0.72-2.98)	1.31 (0.56-2.58)	6.80 (5.30-8.60)	4.90 (3.97-5.97)	6.06 (5.26-6.99)	3.10 (2.00-4.85)
Q2-Spring	0.86 (0.28-2.01)	2.09 (1.11-3.57)	7.41 (5.88-9.21)	5.55 (4.57-6.67)	7.68 (6.77-8.71)	2.41 (1.47-3.97)
Q3-Summer	2.88 (1.68-4.61)	1.26 (0.55-2.49)	11.1 (9.21-13.2)	6.11 (5.10-7.27)	7.82 (6.91-8.86)	2.69 (1.69-4.31)
Q4-Autumn	2.20 (1.17-3.75)	2.68 (1.56-4.28)	8.09 (6.54-9.90)	5.21 (4.27-6.28)	6.31 (5.50-7.25)	2.20 (1.32-3.70)

* data from years 2020 and 2021 are included for informational purposes only: events and follow-up time from these years are not included in the calculations of other incidence rates in the table.

4.3.   Other analyses, including sensitivity analyses

Not applicable.

5. Discussion

5.1.   Key results

There was a variation between databases with incidence rate estimates varying between 1.84 and 8.38 per 100,000 person-years. There was a pronounced increase in the incidence of pemphigoid with increasing age but no clear difference between males and females, except in Germany where the incidence rate was higher in males compared to females. Excluding data from 2020, there was not a clear pattern of a change with time in the incidence of pemphigoid. These figures are broadly in line with published literature.

A recent systematic review and meta-analysis by Persson *et al* (2022) reported an incidence rate for bullous pemphigoid of 3.42 per 100,000 per year based on four studies where there was a true person-time denominator. Separately, the same group also reported a cumulative incidence of 0.82 per 100,000 based on 23 studies where populations were followed-up over one year with incidence calculated as a proportion. Significant heterogeneity was reported between studies.

Coincidentally, a second study (Lu *et al*, 2022) has also recently systematically reviewed and meta-analysed studies reporting incidence rates of bullous pemphigoid, including may of the same studies that Persson *et al (*2022) which reported an overall global incidence of 4.19 per 100,000.

Kridin *et al* (2018) also reviewed studies across different years and populations and found incidence varied from 6.7 to 42.8 per 1,000,000.

The finding of an increasing incidence with increasing age has been widely reported previously (Lee *et al*, 2019; Kridin *et al*, 2018; Persson *et al* 2021). Literature suggests that slightly more pemphigoid occurs in females than males (Lee *et al*, 2019; Kridin *et al*, 2018; Persson *et al*, 2021). Kridin *et al* (2018) also reported several studies showing that the incidence rate seems to be higher in women until the age of 75, but thereafter the incidence was higher in men.

5.2.   Limitations

Diagnostic coding for pemphigoid is not known to have been validated in the primary care databases available. As a skin condition, it is likely to be reported in primary care and would be expected to be recorded accurately. In a recent UK-based paper, Persson *et al* (2021) claimed 93.2% positive predictive value for a study using primary care records, although no data was presented to support this. Although confirmation of the diagnoses required specialist input (incorporating biochemistry and histological investigation), the nature of the diagnosis means that its recording in primary care records could be reasonably accurate. However, this assumption should be treated cautiously.

The results of this study showed evidence of changes in healthcare utilisation during the COVID-19 pandemic (2020-present), which might have the potential to give misleading results. For this reason, data from 2020 and 2021 were not included when producing incidence rates.

It also needs to be considered that the entire patient history may not be included in the data source, and that there is a risk that a prevalent case may have been misclassified as incident. This may result in overestimation of incidence rate.

6. References

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Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

The Health Improvement Network (THIN®) Italy

In THIN® Italy data collection started in 2000 and this database is currently able to provide clinical monitoring data of anonymised patients managed by 500 GPs in primary care (including patients' history). The data source of THIN® Italy is electronic health care records. The entire database reaches 900,000 patients (active and non-active), from which 500,000 are currently actively followed. In order to be representative at national and macroregional level, physicians have been recruited in accordance with their universe distribution in terms of geography, age and gender.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and they are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The Health Improvement Network (THIN®) Romania

THIN® Romania is a primary care healthcare database, including only General Practitioners (574 GPs). The source of data is electronic health care records. Enrolled GPs and their patients are representative of the whole Romanian population in terms of location, demographics and prevalence from the point of view of main chronic health pathologies. Data collection started in 2012.

In Romania, the insured population (background sampled population) numbered 17.1 million individuals (data from 2012). Among these, 8.5 million individuals benefited of healthcare services, in the public system. The number of GPs who worked in the public healthcare system, in 2017 was aproximately 11,000 physicians. They recorded 76 million consultations and issued 71 million prescriptions (data from 2017). The number of deceased patients was of 297,000 individuals, and number of newborns in 2020 was of 179,000 individuals.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and they are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The Health Improvement Network (THIN®) Spain

THIN® Spain is mainly a primary care healthcare database, including practitioners (GP), specialists and pediatricians & nurses. It contains data from approximately 2,000 GPs and 2,400 specialists (cardiology, pulmonology, urology, etc.). THIN® Spain also includes partial activities related to the hospital. THIN® Spain is globally representative of the whole national demographics and prevalence on the main chronic health pathologies. THIN® Spain includes 3,000,000 individuals out of the overall population. Among these, 1,050,000 are active in the previous year and 1,800,000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals. New patients are automatically included into the database, and deceased patients identified in a specific field.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all

countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN® database.

The THIN® Spain Database has been approved by two Ethics Committees, one from the Community of Madrid (Hospital Ramón Cajal) and one from the Community of Catalonia (Hospital Clinic de Barcelona). These ethics committees reviewed the data collection, protection, and anonymization processes and positively approved THIN® Spain for observational research of medical products (upon protocol submission).

Annex 2 - Codelists

THIN® – Italy

code	label
M2IT.ICD9.694.2	DERMATITE ERPETIFORME GIOVANILE
M2IT.ICD9.694.5	PEMFIGOIDE
M2IT.ICD9.694.6	PEMFIGOIDE BENIGNO DELLE MUCOSE
M2IT.ICD9.694.60	PEMFIGOIDE BENIGNO DELLE MUCOSE SENZA MENZIONE DI INTERESSAMENTO OCULARE
M2IT.ICD9.694.61	PEMFIGOIDE BENIGNO DELLE MUCOSE CON INTERESSAMENTO OCULARE

THIN® - Romania

code	label
PHRO.ICD10.L120	Pemphigoid bulos
PHRO.ICD10.L121	Pemphigoid cicatrial
PHRO.ICD10.L122	Dermatoza
PHRO.ICD10.L123	Epidermoliza buloasa dobindita
PHRO.ICD10.L128	Pemphigoid

THIN® – Spain

code	label
FUES.CIE10.L12.0	PENFIGOIDE AMPOLLOSO
FUES.CIE10.L12.1	PENFIGOIDE CICATRICIAL
FUES.CIE10.L12.2	ENFERMEDAD AMPOLLOSA CRÓNICA DE LA INFANCIA
FUES.CIE10.L12.8	OTROS TIPOS DE PENFIGOIDE
FUES.CIE9.694.2	DERMATITIS HERPETIFORME JUVENIL
FUES.CIE9.694.5	PENFIGOIDE
FUES.CIE9.694.6	PENFIGOIDE BENIGNO DE LA MEMBRANA MUCOSA
FUES.CIE9.694.60	PENFIGOIDE BENIGNO MEMBRANA MUCOSA-SIN IMPLICACION OCULAR
FUES.CIE9.694.61	PENFIGOIDE BENIGNO MEMBRANA MUCOSA-CON IMPLICACION OCULAR

IMRD (UK)

clinicalcodeid	term	readtermid
5684019	Acquired epidermolysis bullosa	M1453
10833016	Juvenile dermatitis herpetiformis	M142
57191017	Mucous membrane pemphigoid	M146

57192012	Cicatricial pemphigoid	M1460-1
127980014	Bullous pemphigoid	M1450
142845014	Pemphigoid	M145
308664012	Pemphigoid NOS	M145z
308669019	Benign mucous membrane pemphigoid	M146z
309311010	[X]Other pemphigoid	Myu12
399920011	Benign mucous membrane pemphigoid with no eye involvement	M1460
485794012	Ocular pemphigoid	M1461
267631000006119	Ocular pemphigoid	F4Cy1
403571000006114	[X]Ocular pemphigoid	FyuC6
5128231000006113	Prebullous pemphigoid	^ESCTPR512823
6049801000006118	Ocular cicatricial pemphigoid	^ESCTOC604980

IQVIA™ Disease analyzer – France

ICD10 code	term
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid (Benign mucous membrane pemphigoid)
L12.2	Chronic bullous disease of childhood (Juvenile dermatitis herpetiformis)
L12.3	Acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified

IQVIA™ Disease analyzer – Germany

ICD10 code	term
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid (Benign mucous membrane pemphigoid)
L12.2	Chronic bullous disease of childhood (Juvenile dermatitis herpetiformis)
L12.3	Acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified

Annex 3 – Database specific results

THIN® – Italy

strata		Rate per 100,000 (95% CI)
overall		1.88 (1.37-2.53)
2015		0.67 (0.14-1.95)
2016		1.96 (0.90-3.72)
2017		2.14 (1.03-3.93)
2018		1.05 (0.34-2.44)
2019		3.51 (2.04-5.62)
under 20 years		0.00 (0.00-2.45)
20-29 years		0.00 (0.00-1.55)
30-39 years		0.00 (0.00-1.30)
40-49 years		0.48 (0.06-1.75)
50-59 years		0.71 (0.15-2.07)
60-69 years		1.70 (0.62-3.70)
70-79 years		3.82 (1.91-6.83)
80 years & over		11.69 (7.33-17.70)
Male		1.29 (0.70-2.16)
Female		2.40 (1.62-3.42)
Male	under 20 years	0.00 (0.00-4.80)
Male	20-29 years	0.00 (0.00-3.18)
Male	30-39 years	0.00 (0.00-2.81)
Male	40-49 years	0.52 (0.01-2.87)
Male	50-59 years	0.50 (0.01-2.76)
Male	60-69 years	0.60 (0.02-3.34)
Male	70-79 years	3.84 (1.25-8.97)
Male	80 years & over	8.58 (3.15-18.67)
Female	under 20 years	0.00 (0.00-4.99)
Female	20-29 years	0.00 (0.00-3.05)
Female	30-39 years	0.00 (0.00-2.43)
Female	40-49 years	0.46 (0.01-2.54)
Female	50-59 years	0.90 (0.11-3.25)
Female	60-69 years	2.69 (0.87-6.27)
Female	70-79 years	3.80 (1.39-8.27)
Female	80 years & over	13.53 (7.74-21.98)
Q1 - Winter		1.57 (0.72-2.98)
Q2 - Spring		0.86 (0.28-2.01)
Q3 - Summer		2.88 (1.68-4.61)
Q4 - Autumn		2.20 (1.17-3.75)

THIN® – Romania

strata		Rate per 100,000 (95% CI)
overall		1.84 (1.35-2.45)
2015		2.18 (1.04-4.00)
2016		2.81 (1.53-4.71)
2017		1.35 (0.54-2.78)
2018		2.11 (1.05-3.78)
2019		0.79 (0.22-2.03)
under 20 years		1.46 (0.67-2.78)
20-29 years		1.00 (0.12-3.62)
30-39 years		0.77 (0.09-2.80)
40-49 years		0.30 (0.01-1.70)
50-59 years		1.27 (0.35-3.25)
60-69 years		3.06 (1.58-5.35)
70-79 years		3.89 (1.86-7.15)
80 years & over		4.40 (1.62-9.58)
Male		1.89 (1.17-2.89)
Female		1.79 (1.16-2.65)
Male	under 20 years	1.28 (0.35-3.27)
Male	20-29 years	0.00 (0.00-4.21)
Male	30-39 years	0.93 (0.02-5.21)
Male	40-49 years	0.00 (0.00-2.54)
Male	50-59 years	0.71 (0.02-3.95)
Male	60-69 years	5.39 (2.47-10.24)
Male	70-79 years	3.99 (1.09-10.20)
Male	80 years & over	4.22 (0.51-15.26)
Female	under 20 years	1.65 (0.54-3.86)
Female	20-29 years	1.79 (0.22-6.46)
Female	30-39 years	0.66 (0.02-3.69)
Female	40-49 years	0.55 (0.01-3.04)
Female	50-59 years	1.72 (0.35-5.02)
Female	60-69 years	1.33 (0.27-3.89)
Female	70-79 years	3.83 (1.40-8.33)
Female	80 years & over	4.50 (1.23-11.52)
Q1 - Winter		1.31 (0.56-2.58)
Q2 - Spring		2.09 (1.11-3.57)
Q3 - Summer		1.26 (0.55-2.49)
Q4 - Autumn		2.68 (1.56-4.28)

THIN® – Spain

strata		Rate per 100,000 (95% CI)
overall		8.38 (7.55-9.28)
2015		11.97 (9.49-14.90)
2016		7.63 (5.90-9.71)
2017		6.23 (4.73-8.05)
2018		8.04 (6.36-10.04)
2019		8.99 (7.22-11.06)
under 20 years		2.04 (1.21-3.22)
20-29 years		2.18 (1.04-4.01)
30-39 years		2.11 (1.15-3.54)
40-49 years		1.76 (0.94-3.01)
50-59 years		4.20 (2.74-6.15)
60-69 years		9.30 (6.78-12.44)
70-79 years		25.63 (20.56-31.58)
80 years & over		67.14 (57.05-78.50)
Male		8.70 (7.49-10.06)
Female		8.09 (6.97-9.34)
Male	under 20 years	1.11 (0.36-2.58)
Male	20-29 years	1.84 (0.50-4.71)
Male	30-39 years	2.58 (1.11-5.08)
Male	40-49 years	1.93 (0.78-3.97)
Male	50-59 years	4.02 (2.08-7.03)
Male	60-69 years	12.61 (8.44-18.11)
Male	70-79 years	31.70 (23.52-41.79)
Male	80 years & over	81.00 (63.03-102.5)
Female	under 20 years	3.02 (1.61-5.16)
Female	20-29 years	2.48 (0.91-5.41)
Female	30-39 years	1.70 (0.62-3.70)
Female	40-49 years	1.59 (0.59-3.47)
Female	50-59 years	4.36 (2.38-7.32)
Female	60-69 years	6.30 (3.60-10.23)
Female	70-79 years	20.47 (14.49-28.10)
Female	80 years & over	59.20 (47.48-72.93)
Q1 - Winter		6.80 (5.30-8.60)
Q2 - Spring		7.41 (5.88-9.21)
Q3 - Summer		11.05 (9.21-13.16)
Q4 - Autumn		8.09 (6.54-9.90)

IMRD (UK)

strata	Rate per 100,000 (95% CI)
overall	5.44 (4.95-5.97)
2015	5.33 (4.23-6.62)
2016	4.80 (3.78-6.00)
2017	6.40 (5.24-7.74)
2018	5.38 (4.34-6.60)
2019	5.29 (4.26-6.48)
under 20 years	0.21 (0.06-0.54)
20-29 years	0.88 (0.40-1.67)
30-39 years	0.66 (0.28-1.30)
40-49 years	1.21 (0.66-2.02)
50-59 years	2.09 (1.33-3.14)
60-69 years	7.05 (5.35-9.12)
70-79 years	19.60 (16.22-23.47)
80 years & over	54.55 (47.47-62.39)
male	5.33 (4.65-6.08)
female	5.56 (4.86-6.33)
male under 20 years	0.20 (0.02-0.74)
male 20-29 years	0.59 (0.12-1.73)
male 30-39 years	0.33 (0.04-1.19)
male 40-49 years	1.00 (0.37-2.17)
male 50-59 years	1.24 (0.50-2.56)
male 60-69 years	7.59 (5.16-10.77)
male 70-79 years	21.03 (16.05-27.07)
male 80 years & over	68.62 (56.29-82.85)
femaleunder 20 years	0.22 (0.03-0.79)
female20-29 years	1.16 (0.42-2.52)
female30-39 years	0.99 (0.36-2.15)
female40-49 years	1.43 (0.62-2.82)
female50-59 years	2.99 (1.71-4.86)
female60-69 years	6.52 (4.30-9.49)
female70-79 years	18.30 (13.90-23.66)
female80 years & over	45.05 (36.85-54.54)
Q1 - Winter	4.90 (3.97-5.97)
Q2 - Spring	5.55 (4.57-6.67)
Q3 - Summer	6.11 (5.10-7.27)
Q4 - Autumn	5.21 (4.27-6.28)

IQVIA™ Disease analyzer – France

Strata	IR per 100,000 Person-years (95% CI)
overall	2.60 (2.04 - 3.31)
2015	2.26 (1.24 - 4.15)
2016	2.58 (1.52 - 4.42)
2017	1.71 (0.91 - 3.25)
2018	2.27 (1.31 - 3.96)
2019	4.18 (2.74 - 6.39)
0-19 years	0.00 (0.00 - 0.63)
20-29 years	0.38 (0.09 - 2.09)
30-39 years	0.97 (0.35 - 2.85)
40-49 years	0.29 (0.07 - 1.60)
50-59 years	2.64 (1.41 - 5.01)
60-69 years	2.64 (1.36 - 5.20)
70-79 years	5.77 (3.33 - 10.09)
80+ years	21.46 (15.16 - 30.47)
female	2.42 (1.72 - 3.41)
male	2.80 (2.00 - 3.93)
female 0-19 years	0.00 (0.00 - 1.32)
female 20-29 years	0.00 (0.00 - 2.52)
female 30-39 years	1.74 (0.63 - 5.08)
female 40-49 years	0.00 (0.00 - 2.00)
female 50-59 years	2.25 (0.91 - 5.75)
female 60-69 years	2.49 (1.01 - 6.38)
female 70-79 years	3.57 (1.45 - 9.13)
female 80+ years	19.24 (12.07 - 30.80)
male 0-19 years	0.00 (0.00 - 1.22)
male 20-29 years	0.83 (0.20 - 4.65)
male 30-39 years	0.00 (0.00 - 2.72)
male 40-49 years	0.61 (0.15 - 3.42)
male 50-59 years	3.07 (1.35 - 7.16)
male 60-69 years	2.80 (1.14 - 7.18)
male 70-79 years	8.36 (4.30 - 16.47)
male 80+ years	24.97 (14.98 - 41.90)
Q1 - Winter	3.10 (2.00 - 4.85)
Q2 - Spring	2.41 (1.47 - 3.97)
Q3 - Summer	2.69 (1.69 - 4.31)
Q4 - Autumn	2.20 (1.32 - 3.70)

IQVIA™ Disease analyzer – Germany

Strata	IR per 100,000 Person-years (95% CI)
overall	6.97 (6.53 - 7.45)
2015	6.66 (5.70 - 7.78)
2016	6.78 (5.83 - 7.89)
2017	7.55 (6.56 - 8.69)
2018	6.90 (5.98 - 7.97)
2019	6.95 (6.01 - 8.05)
0-19 years	2.05 (1.32 - 3.19)
20-29 years	0.93 (0.55 - 1.59)
30-39 years	1.02 (0.63 - 1.65)
40-49 years	1.28 (0.85 - 1.91)
50-59 years	2.85 (2.25 - 3.61)
60-69 years	6.89 (5.82 - 8.18)
70-79 years	13.38 (11.70 - 15.31)
80+ years	36.98 (33.54 - 40.79)
female	8.06 (7.40 - 8.77)
male	5.76 (5.19 - 6.41)
female 0-19 years	2.63 (1.52 - 4.60)
female 20-29 years	1.14 (0.59 - 2.24)
female 30-39 years	1.11 (0.59 - 2.10)
female 40-49 years	1.92 (1.22 - 3.03)
female 50-59 years	3.51 (2.61 - 4.72)
female 60-69 years	7.19 (5.72 - 9.06)
female 70-79 years	13.51 (11.28 - 16.19)
female 80+ years	38.31 (33.92 - 43.27)
male 0-19 years	1.48 (0.73 - 3.05)
male 20-29 years	0.72 (0.32 - 1.69)
male 30-39 years	0.92 (0.45 - 1.90)
male 40-49 years	0.58 (0.25 - 1.35)
male 50-59 years	2.16 (1.47 - 3.18)
male 60-69 years	6.56 (5.11 - 8.45)
male 70-79 years	13.23 (10.83 - 16.17)
male 80+ years	34.78 (29.50 - 41.02)
Q1 - Winter	6.06 (5.26 - 6.99)
Q2 - Spring	7.68 (6.77 - 8.71)
Q3 - Summer	7.82 (6.91 - 8.86)
Q4 - Autumn	6.31 (5.50 - 7.25)