EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2023

Data analysis plan

Title: Incidence rates of pemphigus and pemphigoid following COVID-19 vaccines

Administrative details of the data analysis	
Substance(s)	Comirnaty / Spikevax / Vaxzevria
Condition/ADR(s)	Pemphigus and pemphigoid
Short title of topic	Incidence rates of pemphigus and pemphigoid
TDA-DAT lead analyst (and reviewer)	Robert Flynn (Maria Clara Restrepo-Mendez)

1. List of abbreviations

MAH	*Marketing Authorisation Holder*
EMA	*European Medicines Agency*
PRAC	*Pharmacovigilance Risk Assessment Committee*
RDA	*Rapid Data Analysis*

2. Rationale and background

Pemphigus and pemphigoid are autoantibody-mediated blistering diseases of the skin or mucous membranes. Pemphigus affects the epidermis and causes lesions and blisters that are easily ruptured. Pemphigoid affects a lower layer of the skin, between the epidermis and the dermis, creating tense blisters that do not break easily. [1] Over-active immune system leads to skin cells separating from each other, fluid collecting between skin layers and blisters formation. [1] There are several different types of pemphigus: Pemphigus Vulgaris (PV), Pemphigus Foliaceus, Pemphigus Vegetans, IgA Pemphigus, Paraneoplastic Pemphigus, Mucous Membrane Pemphigoid, Bullous Pemphigoid (BP), Gestational Pemphigoid, Epidermolysis Bullosa Acquisita.[1]

The pathogenesis of the conditions depends on the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors. Most of cases of pemphigoid are considered idiopathic, however, several trigger factors have been described in literature, such as UV light, radiation, drugs, and trauma. [2] Some studies have suggested a potential link between the development of autoimmune bullous diseases and vaccines such as influenza, hepatitis B, typhoid, tetanus, anthrax. However, the current evidence remains limited, and findings need to be confirmed in large-scale, population-based studies. [2, 3] Cases of immunobullous disease developed after COVID-19 vaccine injection have recently been reported, with a variable latency time, mostly <1 month. [4, 5]

During routine signal detection activities, cases of pemphigus and pemphigoid in close temporal association to Comirnaty, Spikevax and Vaxzevria vaccination were identified in EudraVigilance and the scientific literature. To support the assessment of the signal, estimates on incidence rates for pemphigus and pemphigoid are generated in the general and vaccine-exposed population across relevant electronic health record databases available within the Agency with data on COVID-19 vaccines.

3. Research question and objectives

This study aims to describe:

i. Comirnaty, Spikevax and Vaxzevria vaccine exposure: overall and stratified by sex, age, and year.

ii. Incidence rates of new onset pemphigus or pemphigoid (or related conditions) in the general population: overall and stratified by sex, age, and year.

iii. Incidence rates of new onset pemphigus or pemphigoid (or related conditions) following exposure to Comirnaty, Spikevax or Vaxzevria vaccines stratified by number of doses. If there are a sufficient number of events, this will also be stratified by age and sex.

4. Research methods

4.1. Study design

This will be a cohort study describing vaccine exposure, population incidence rates of pemphigus and pemphigoid, and incidence rates of pemphigus and pemphigoid in the vaccine exposed population.

4.2. Data sources

The following databases will be used: **IQVIA™ Medical Research Data (IMRD) UK** and **THIN® Spain**. Brief descriptions of these databases are provided in **Annex 1**. Other available data sources at EMA do not capture COVID-19 vaccines sufficiently completely or accurately.

4.3. Setting and study population

The study population will be the general population in the UK and patients visiting general practices (GPs) in Spain.

4.4. Study period

The study period will vary according to the years of coverage in the two databases:

- For IMRD UK database, the covered period will be from 2009 to 2022.
- For THIN® Spain, the covered period will be from 2014 to 2022.

N.B.: For each, background (population) incident rates will be calculated during the pre-pandemic period (up to and including 2019) and post-vaccination event rates will be estimated from 2020 onwards.

4.5. Variables

Exposure

In IMRD UK database, COVID-19 vaccine exposures are identified as prescribed medicines with data captured by point of care systems accredited to support the delivery of COVID-19 vaccinations: this is automatically fed back into the GP clinical system. A good level of completeness for recording of

COVID-19 vaccination status and dates of dose are expected, although it is not known if this has been validated for research purposes.

In the THIN® Spain database, vaccine exposure will be identified from the bespoke vaccination data table.

In the IMRD UK, the most widely used vaccines were Comirnaty and Vaxzevria. In THIN® Spain, the most widely used vaccines were Comirnaty and Spikevax followed by Vaxzevria.

Annex 2 shows the codes that will be used for each database to identify COVID-19 vaccination status.

Outcome

Pemphigoid and pemphigus will be identified through Read codes for IMRD UK database and ICD10 codes for THIN® Spain database. As spontaneous reports have identified a variety of autoimmune bullous disorders as being associated with use of COVID-19 vaccines, - this analysis will cover bullous pemphigoid, pemphigus vulgaris and related blistering conditions.

The case definitions used will be tested in a sensitivity analysis, with the primary analysis consisting of a narrow definition based on ICD10 codes L10 (pemphigus) and L12 (pemphigoid). In a sensitivity analysis, we will explore a broader definition covering bullous conditions more generally also including related conditions and differential diagnoses (L11 other acantholytic disorders and L13 Other bullous disorders). **Annex 2** provides the list of codes for the narrow and broad definitions.

Other variables

- Vaccine utilisation will be stratified by sex, age (at first use), and year of vaccination.

  Age will be categorised as: **<30; 30-39; 40-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-79; 80-84; ≥85** years.
- Event rates for pemphigoid and pemphigus in the general population will be stratified by sex, age and year of recorded diagnosis.
- Event rates among exposed patients will be stratified by number of doses.

4.6. Statistical analysis

4.6.1. Main statistical methods

i. Vaccine exposure: We will describe vaccine exposure as counts of patients who received Comirnaty, Spikevax or Vaxzevria vaccine: overall counts and stratified by sex, age (at first use), and year of vaccination.

Some initial counts of available data according to database are described below:

	Comirnaty		Vaxzevria		Spikevax	
	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations
IMRD UK	1,059,011	1,976,221*	561,761	1,091,652**	331,256	386,737**

THIN® Spain	644,786	1,335,356*	126,983	244,615**	435,573	612,119**

* Coverage across all age groups. ** Limited use in older age groups

Comirnaty will be covered by both IMRD UK and THIN® Spain.

Data on Vaxzevria vaccine will mainly come from the IMRD UK, as Vaxzevria was widely used in the early months of the UK vaccination campaign.

Spikevax is used in both IMRD UK and THIN® Spain; however, as this vaccine was commonly used after others (i.e., as a second or subsequent dose), data coverage is expected to be more limited.

ii. Event rates in the general population: We will describe the incidence of new onset of pemphigoid or pemphigus (or related conditions) in patients contributing patient time to the databases listed above in the years pre-dating the COVID-19 vaccination campaigns (up to 2019).

Patients will be 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 will be **excluded** from the analysis if they have any prior history of any of the selected codes for pemphigoid or pemphigus (or related conditions) in the database.

Analysis:

Numerator: The numerator will consist of the number of patients who experience the event of interest (pemphigoid, pemphigus or related conditions) during the (yearly) time period. Patients with a baseline history of pemphigoid and pemphigus will be excluded. Included patients will be allowed to contribute only one event each.

Denominator: The denominator will be defined as **patient follow-up time**. As with the numerators, patients with a baseline history of pemphigoid and pemphigus at the start of each period will be excluded. Patient follow-up time will be truncated at the earliest date of the following: a) the occurrence of the first event (pemphigoid, pemphigus or related conditions) after which they will not contribute to the analysis, b) death of patient, c) end of the observation period (i.e., end of data availability because the patient moved practice, or reached the end of follow-up for their practice), or d) end of study period.

Follow-up time will be calculated using the following formula:

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

The **incidence rate** for pemphigoid and pemphigus (or related conditions) will be defined as the number of events divided by the total follow up time. The incidence rate will be calculated using the following formula:

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

The incidence rate will be presented as the number of events per 100,000 person-years.

Confidence intervals around incidence rates will be calculated using exact method.

iii. Standardised event rates in the general population: To compare event rates between COVID-19 vaccines, event rates (see **section ii**) will be standardised by age and sex to a standard European reference population [6]. This is because COVID-19 vaccines were typically used in different age groups across countries and pemphigoid and pemphigus seem to be less common in younger age groups.

iv. Standardised event rates among exposed patients: To describe the event rate of new onset pemphigoid or pemphigus (or related conditions) following exposure to the vaccine, event rates will be calculated using the same methodology described in sections **(ii)** and **(iii)** above but restricted to only those patients known to have been exposed to the vaccines.

N.B.: The time to onset described in spontaneous reports is typically between 1 day and one month. - However, the presentation in the real-world clinical setting is unpredictable. For instance, bullous pemphigoid (the most common type found in our databases) is characterised by an initial pre-bullous phase with nonspecific symptoms such as pruritic lesions which may last for several weeks to months, delaying the diagnosis. [2, 7] Diagnosis then involves referral to secondary care and requires confirmation by serology/histology which means that time to diagnosis can take many weeks or months. Therefore, **exposed patients will be followed up for a maximum of 90-day following first exposure**, a cut-off subject to sensitivity analyses. The incidence rate will be calculated as new onset events divided by the total duration of follow-up time in years. These incidence rates will also be standardised by age and sex to a standard European reference population [6].

Patients will be **excluded** from the analysis if they have a history of use of the other COVID-19 vaccines and will be censored from the analysis if they leave the population (i.e., moved practice, die, or reached the end of follow-up for their practice), or when they are exposed to an alternative COVID-19 vaccine. This means that patient follow-up time will only consist of follow-up time with a history of a single type of COVID-19 vaccine.

The **primary analysis** will consider the **90-day period after the initial vaccine**. A secondary analysis will look at the second and subsequent exposures to the vaccine.

4.6.2. Exploratory analysis: Self-controlled Case Series

The use of a Self-controlled Case Series (SCCS) design will be explored [8,9] as this signal involves a transient exposure for which risk windows can reliably be constructed. The self-controlled case series design method relies on comparisons within people in a population of individuals who have both the outcome and exposure of interest. [8,9] Incidence rate ratios are derived comparing the rate of events during exposed periods of time with the rate during all other observed time periods. A major advantage of this design is that the potential confounding effect of both recorded and unrecorded characteristics that vary between individuals, but are fixed over time within individuals, is removed [8,9] (i.e., comparisons are made within individuals, therefore, individuals act as their own control).

For this study, we will identify all patients with at least one incident pemphigoid or pemphigus (or related conditions) during the follow-up time (**from 01Jan2019 to 01Jun2022**) and exposed to Comirnaty, Spikevax or Vaxzevria vaccines. Patients with a history of events predating this period will be included in the analysis. Periods of follow-up with no exposure to Comirnaty will be classified as "unexposed window". Follow-up will not be censored at the occurrence of the event, as later exposed and unexposed periods of time will be included in the

analysis. Risk periods will be defined as 90-day periods after a vaccine exposure. The length of the "unexposed" periods will vary for each patient. The null hypothesis will be that the incidence of pemphigoid or pemphigus (or related conditions) remains constant during the time periods and is not affected by exposure to Comirnaty Spikevax or Vaxzevria vaccines.

The key elements of this analysis are described below.

Data source: IMRD UK (and possibly THIN® Spain which has data for Spikevax)

Study cohort: Patients vaccinated with Comirnaty, Vaxzevria or Spikevax AND with a diagnosis of pemphigoid or pemphigus (or related conditions) from 2019 onwards. Follow-up starts 1-year (observation time) after first entry onto database.

Event definition: As defined in section 5.5 above. In this analysis, repeated events will be allowed. Although potentially self-limiting, acute bullous disorders are chronic conditions with a clinical course that may last from months to years, and which have a high tendency to relapse. [2, 7] Therefore, **it is difficult to define a time period between which consecutive codes for the same condition represent a relapse or the continuation of the same ongoing episode**. In the primary analysis, events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) will be assumed to be a single event starting on the earliest date.

Risk window: 90 days.

Censored date: Death, end of follow-up on database (deregistration, date of last collection), use of other COVID-19 vaccine.

Risk "windows":

Pre-vaccination "unexposed":	**from** 01Jan2019 (or date of entry onto database) **to** first exposure
1st vaccination "exposed":	**from** 1st vaccination date **to** 1st vaccination date + 90 days (or censored)
Post-vaccination "unexposed":	**from** 1st vaccination date + 90 days **to** 2nd vaccination (or censored)
Subsequent vaccination "exposed":	**from** n^{th} vaccination date **to** n^{th} vaccination date + 90 days (or censored). Consecutive vaccinations within the risk window to be coalesced into a single window.
Subsequent post-vaccination "unexposed":	**from** n^{th} subsequent vaccination date + 90 days **to** n^{th} subsequent vaccination (or censored)

Multiple subsequent vaccination episodes can be incorporated (n^{th} vaccinations). Pre- and post-initial vaccination "at risk" periods will be evaluated separately (to see if there is any evidence that the effect is not transient) and combined if appropriate.

The following assumptions are implicit in the analysis:

- Given the relatively short study duration, potential confounding by age is unlikely to be an issue; however, this will be considered in an adjusted model using Poisson regression (see Methods below).
- Occurrence of the event is not expected to influence subsequent likelihood of vaccination.

- Occurrence of the event does not prohibit subsequent vaccination.
- Occurrence of the event is not associated with increased risk of death.
- Event rates are constant within time windows: the outcome event codes are used reasonably consistently between 2019 and 2022.

Methods: We will compare event rates (n events / follow-up time) in not-at-risk "unexposed" time windows with at risk "exposed" time windows. We will model event rates using a conditional Poisson regression to obtain a relative incidence rate. In an additional model, we will adjust by age. In addition, we will compare initial "at-risk" window with subsequent "at-risk" windows. The period covered will be from **01 January 2019 to 01 June 2022**.

4.6.3. Sensitivity analysis

For the **main analysis**, sensitivity analyses will include:

- Calculating event rates in exposed subjects over **180 days follow-up post vaccination** (as opposed to 90 days). Additional follow-up periods will be explored.
- Using a **broader endpoint definition** of pemphigoid or pemphigus-related conditions. See **Annex 2** for details.

For the **explorative analysis** (self-controlled case series), we will estimate event rates using (in order of priority):

- A **180-day risk window** (instead of 90 days). Additional follow-up periods will be explored. Risk windows will also be reduced to explore when events might occur following vaccination
- A **broader endpoint definition** of pemphigoid or pemphigus-related conditions. See **Annex 2** for details.
- Exclude patients with history of event at study entry
- Exclude patients with history of event at study entry and limit outcome to the first (incident) event only
- Test the 180-day cut-off for discrete events by reducing to 90 days and extending to 365 days
- Exclude patients who do not survive to end of follow-up (01Jun2022)
- Exclude patients exposed to medicines that are considered likely to be associated bullous disorders during the study period [10]: this is a potential time-dependant bias.

Analyses will be done using SAS for IMRD UK and THIN® Spain.

Tables shell 1 to 5 **(Annex 3)** illustrate the estimates that will be provided for the main, explorative and sensitivity analyses.

4.7. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be 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 will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4.8. Limitations of the research methods

For the THIN® Spain database, denominators are not based on true population denominators. Instead, they are based on patients with health encounters. Patients included in incidence calculations are required to have at least one year between the first and the last visit and one year of lead-in time.

Incomplete ascertainment of vaccine exposure as a prescribed medicine is a potential issue in all data sources. Vaccines covered by national vaccination schemes might, however, be administered without an individual patient prescription or the vaccine might be administered outside of the GP practice, and such vaccinations might not be recorded in the databases. Thus, these data may play a subordinate role, particularly for vaccinations covered by the national health insurance (NHI), and the extent to which the available information in our databases reflects the true use of the vaccines of interest in the population is unknown. It is also possible that the vaccine utilization pattern is different in patients who have received the vaccine through a prescription compared to all patients who have received the vaccine. Hence, the generalizability of our results may be limited. In the IMRD UK database, COVID-19 vaccination data has been captured by accredited point of care systems designed to support the delivery of the vaccination campaign, which is automatically fed back into the GP clinical system. A high level of completeness of recording of COVID-19 vaccination status in GP software is expected, although we are not aware if this has been validated.

Uncertainly about the completeness of the ascertainment of exposure and a high level of uptake of the vaccines at a population level means that a meaningful unexposed cohort cannot be identified, so a comparative analysis against unexposed patients is not possible. For this reason, we have proposed the approach of using the SCCS study design.

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 study [11], 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.

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.

5. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

6. Management and reporting of adverse events/adverse reactions

Pursuant to the requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

7. Plans for disseminating and communicating study results

The analysis plan and study results will be published in EUPAS registry upon completion.

8. 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.

The Health Improvement Network (THIN®) Spain

The Health Improvement Network (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 study protocol for this study has been submitted to and approved by Hospital Clinic de Barcelona ethics committee, who reviewed the data collection, protection, and anonymization processes.

In addition to this study, THIN® Spain had previously received protocol approval in the scope of other observational study by two ethics committees (Hospital Ramón Cajal, Madrid, and Hospital Clinic, Barcelona).

Annex 2 – Codelists

Table A1. Codes use to identify COVID-19 vaccine exposure in IMRD UK database

Code	Clinical term
13739541000033114	Comirnaty COVID-19 mRNA Vaccine 30micrograms/0.3ml dose concentrate for dispersion for injection multidose vials (Pfizer Ltd)
13959841000033119	Comirnaty Children 5-11 years COVID-19 mRNA Vaccine 10micrograms/0.2ml dose concentrate for dispersion for injection multidose vials (Pfizer Ltd)
13739441000033113	COVID-19 Vaccine Vaxzevria (ChAdOx1 S [recombinant]) 5x10,000,000,000 viral particles/0.5ml dose suspension for injection multidose vials (AstraZeneca UK Ltd)
13959941000033110	COVID-19 Vaccine Covishield (ChAdOx1 S [recombinant]) 5x10,000,000,000 viral particles/0.5ml dose solution for injection multidose vials (Serum Institute of India)
13979741000033114	COVID-19 Vaccine AZD2816 AstraZeneca (ChAdOx1 nCOV-19)

Table A2. Codes use to identify COVID-19 vaccine exposure in THIN® Spain database

Vaccine Code
FUES.COVID-ASTRAZENECA
FUES.COVID-MODERNA
FUES.COVID-PFIZER

Table A3. Codes use to identify pemphigoid and pemphigus in IMRD UK database

Read code	Clinical term
Narrow endpoint case definition	
M144	Pemphigus
M1450	Bullous pemphigoid
M145	Pemphigoid
M07y2	Dermatitis vegetans
F4Cy1	Ocular pemphigoid
M1448	Drug-induced pemphigus
M145z	Pemphigoid NOS
M146z	Benign mucous membrane pemphigoid
Myu12	[X]Other pemphigoid
^ESCTPE389946	Pemphigoid gestationis
M1460	Benign mucous membrane pemphigoid with no eye involvement
M1461	Ocular pemphigoid
M1453	Acquired epidermolysis bullosa
M146	Mucous membrane pemphigoid
M1460-1	Cicatricial pemphigoid
^ESCTOC604980	Ocular cicatricial pemphigoid
M1443	Pemphigus foliaceous
M1446	Pemphigus vulgaris
Broad endpoint case definition covering bullous conditions more generally (codes to be included *in addition* to those above)	
PH331-1	Benign familial chronic pemphigus
M141-1	Sneddon - Wilkinson disease
M140	Dermatitis herpetiformis
M14	Bullous dermatoses
2F62	O/E - skin bullae present
2F63	O/E - serous bullae
2F65	O/E - haemorrhagic bullae
2F6Z	O/E - skin bullae NOS
^ESCTGR278243	Grover's disease
M229	Transient acantholytic dermatosis
M1440	Benign pemphigus
Myu11	[X]Other specified acantholytic disorders
Myu13	[X]Other specified bullous disorders
Myu15	[X]Acantholytic disorder, unspecified
M21y7	Acquired keratosis follicularis
M147	Erosive pustular dermatosis of the scalp
^ESCTFA379237	Familial benign pemphigus
2F6	O/E - skin bullae
2F6	O/E - skin bullae

^ESCTLA405489	LAD - Linear IgA disease
M141	Subcorneal pustular dermatosis
^ESCTPR512823	Prebullous pemphigoid
^ESCTHE524436	Herpetiform eruption
Related codes not included	
68E0	Pemphigus/pemphigoid screening
43mb	Pemphigus antibody level
43mc	Pemphigoid antibody level
M143	Impetigo herpetiformis
M2y04-1	Sneddon's syndrome

Table A4. Codes use to identify pemphigoid and pemphigus in THIN® Spain database

Diagnostic code	**Clinical term** (ICD10 equivalent)
Narrow endpoint case definition	
FUES.CIE9.694.2	JUVENILE DERMATITIS HERPETIFORMIS (L12.2)
FUES.CIE9.694.4	PEMPHIGUS (L10.0)
FUES.CIE9.694.5	PEMPHIGOID (L12.0)
FUES.CIE9.694.6	BENIGN MUCOUS MEMBRANE PEMPHIGOID (L12.1)
FUES.CIE9.694.60	BENIGN MUCOUS MEMBRANE PEMPHIGOID - WITHOUT OCULAR INVOLVEMENT (L12.1)
FUES.CIE9.694.61	BENIGN MUCOUS MEMBRANE PEMPHIGOID - WITH OCULAR INVOLVEMENT (L12.1)
Broad endpoint case definition covering bullous conditions more generally (codes to be included *in addition* to those above)	
FUES.CIE9.694	BULLOUS DERMATOSES (L13.9)
FUES.CIE9.694.0	DERMATITIS HERPETIFORMIS (L13.0)
FUES.CIE9.694.1	SUBCORNEAL PUSTULAR DERMATOSIS (L13.1)
FUES.CIE9.694.8	OTHER SPECIFIED BULLOUS DERMATOSES (L13.8)
FUES.CIE9.694.9	UNSPECIFIED BULLOUS DERMATOSES (L13.9)
Related code not included	
FUES.CIE9.694.3	IMPETIGO HERPETIFORMIS (L40.1)

Annex 3 – Table shells

Table shell 1. Number of patients with a prescription for COVID-19 vaccines and number of vaccinations: overall and stratified by age and year

	IMRD EMIS UK				THIN Spain					
	Comirnaty		Vaxzevria		Comirnaty		Spikevax		Vaxzevria	
	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations
Overall										
Sex										
Female										
Male										
Age at first use (years)										
<30										
30-39										
40-49										
50-54										
55-59										
60-64										
65-69										
70-74										
75-79										
80-84										
≥85										
Year										
2020										
2021										
2022										

Table shell 2. Incidence rates of new onset pemphigoid and pemphigus in the general population per 100,000 person-years of follow-up: overall and stratified by age groups

Strata	IMRD EMIS UK			THIN Spain		
	Events	Follow-up time (person years)	Rate per 100,000 (95% CI)	Events	Follow-up time (person years)	Rate per 100,000 (95% CI)
Overall						
Sex						
Female						
Male						
Age at first use (years)						
<30						
30-39						
40-49						
50-54						
55-59						
60-64						
65-69						
70-74						
75-79						
80-84						
≥85						
Year						
2009						
…						
2018						
2019						

Table shell 3. Non-standardised and standardised incidence rates of new onset pemphigoid and pemphigus in the general population per 100,000 person-years of follow-up

Strata	Events	Follow-up time (person years)	Overall population event rates	
			Non-standardised	Standardised
			Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)
IMRD UK				
THIN Spain				

Table shell 4. Standardised incidence rates of new onset pemphigoid and pemphigus per 100,000 years of follow-up following exposure to COVID-19 vaccines

Database / event definition	Vaccine	Vaccine window	After receiving first dose			After receiving second dose			After receiving third dose		
			Events*	Follow-up time (person years)	Rate per 100,000 (95% CI)	Events*	Follow-up time (person years)	Rate per 100,000 (95% CI)	Events	Follow-up time (person years)	Rate per 100,000 (95% CI)
IMRD UK	Comirnaty	90-day									
	Vaxzevria	90-day									
	Comirnaty	180-day									
	Vaxzevria	180-day									
THIN Spain	Comirnaty	90-day									
	Spikevax	90-day									
	Vaxzevria	90-day									
	Comirnaty	180-day									
	Spikevax	180-day									
	Vaxzevria	180-day									

Table shell 5. Self-controlled case series (SCCS) analysis: Association between exposure to Comirnaty vaccine and pemphigoid and pemphigus in the ***IMRD EMIS UK database***

Exposure	Events	Follow-up time (person years)	Incidence rate (95% CI)	Relative risk (95% CI)
Unexposed window periods				--
90-day post-exposed window periods				--
Post-exposed window / Unexposed window	--	--	--	