07 March 2023

Data analysis report

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
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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, 3] 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, 4] Cases of immunobullous disease developed after COVID-19 vaccine injection have been reported as well, with a variable latency time, mostly <1 month. [5, 6]

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 current signal, we generated estimates on incidence rates for pemphigus and pemphigoid 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 objectives

This study aimed 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 in the general population: overall and stratified by sex, age, and year.

iii. Incidence rates of new onset pemphigus or pemphigoid following exposure to Comirnaty, Spikevax or Vaxzevria vaccines stratified by number of doses.

4. Research methods

4.1. Study design

This was 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 were used: **IQVIA™ Medical Research Data (IMRD) UK** and **THIN® Spain**. Brief descriptions of these databases are provided in **Annex 1**. Other data sources available at EMA do not capture COVID-19 vaccines in a sufficiently complete or accurate manner.

4.3. Setting and study population

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

4.4. Study period

The study period varied according to the years of data coverage in the two databases:

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

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

4.5. Variables

Exposure

In IMRD UK database, COVID-19 vaccine exposures were identified as prescribed medicines with data captured by point of care systems accredited to support the delivery of COVID-19 vaccinations. These data are automatically fed back into the GP clinical system. In the IMRD UK database, the most widely used vaccines were Comirnaty and Vaxzevria.

In the THIN® Spain database, vaccine exposure was identified from the bespoke vaccination data table. In this database, the most widely used vaccines were Comirnaty and Spikevax followed by Vaxzevria.

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

Outcome

Pemphigoid and pemphigus were 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 covered bullous pemphigoid, pemphigus vulgaris and related blistering conditions.

The case definitions used were 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 explored a broader definition covering bullous conditions more generally – i.e., including related conditions and differential diagnoses (L11 other acantholytic disorders and L13 Other bullous disorders). **Annex 2** provides the list of codes included for the **narrow and broad endpoint definitions**.

Other variables

- Vaccine utilisation was stratified by sex, age (at first use), and year of vaccination.
- Age was categorised as: <30; 30-39; 40-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-79; 80-84; ≥85 years. Bullous pemphigoid (the most common type found in our databases) usually occurs after the sixth to seventh decade, younger people are rarely affected. Therefore, we combined younger age categories (<30 years) for this analysis.
- Event rates for pemphigoid and pemphigus in the general population were stratified by sex, age group, and year of recorded diagnosis.
- Event rates among exposed patients were stratified by number of doses.

4.6. Statistical analysis

4.6.1. Main statistical methods

i. Vaccine exposure: We described overall counts of patients who were exposed to Comirnaty, Spikevax or Vaxzevria vaccines and overall counts of vaccines administered in the IMRD UK and THIN® Spain databases. We also presented these absolute frequencies stratified by sex, age (at first use), and year of vaccination.

ii. Event rates in the general population: We estimated the incidence of new onset of pemphigoid or pemphigus in patients contributing patient-time to the databases listed above in the years pre-dating the COVID-19 vaccination campaigns (up to and including 2019). Patients were required to have a minimum **observation time of 365 days prior** to entering 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 any of the selected codes for **pemphigoid or pemphigus** in the databases at the start of each period (year).

Calculation of incidence rates:

Numerator: The numerator consisted of the number of new onset events of interest (pemphigoid or pemphigus) during the (yearly) time period. Included patients contributed only one event each.

Denominator: The denominator was defined as **patient follow-up time,** which was expressed in **person-years**. It is the sum of the periods of time-at-risk for each of the patients included in the study cohort. Each patient contributed only as many years of observation to the population at risk as the period over which that **subject was observed to be at risk** of the disease. Follow-up time was truncated at the earliest date of the following: a) the occurrence of the first event (pemphigoid or pemphigus) after which they did 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.

Thus, follow-up time (in years) for each patient was calculated using the following formula:

$$Follow-up\ time\ = \frac{(end\ date\ for\ follow\ up\ period\ -[start\ date\ for\ follow\ up\ period\ +\ 1])}{365.25}$$

The denominator for the incidence rate represents the sum of all the follow-up time for each patient (i.e., total follow-up time).

The **incidence rate** for pemphigoid or pemphigus was defined as the number of new onset events divided by the total follow-up time. The incidence rate was calculated using the following formula:

$$Incidence\ rate = \frac{Number\ of\ new\ onset\ events}{Total\ follow-up\ time\ (years)}$$

The incidence rate is presented as the number of events per 100,000 person-years. Confidence intervals around incidence rates were calculated using exact method.

iii. Standardised event rates in the general population: To allow comparison among COVID-19 vaccines, event rates (see **section ii**) were standardised by age and sex to a standard European reference population [7]. This is because COVID-19 vaccines were typically used in different age groups across countries.

iv. Standardised event rates among exposed patients: To describe the event rate of new onset pemphigoid or pemphigus following exposure to the vaccine, incidence rates were 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 has been between one and 30 days. However, the presentation (i.e., time of diagnosis and recording) 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, 8] 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 were followed up for a maximum of 90-day following first exposure**. This cut-off point was subject to sensitivity analyses (see section 5.6.3).

The **incidence rate** was calculated as new onset events divided by the total duration of follow-up time in years. Patients were **excluded** from the analysis if they had a history of use of the other COVID-19 vaccines. Patients were **censored** from the analysis if they left the population (i.e., moved practice, die, or reached the end of follow-up for their practice), or when they were exposed to an alternative COVID-19 vaccine. This means that **patient follow-up time only consisted of follow-up time with a history of a single type of COVID-19 vaccine**.

These incidence rates were also standardised by age and sex to a standard European reference population [7].

The **primary analysis** considered the **90-day period after the initial vaccine**. Of note, events that occur within both vaccine windows, e.g., the first and second vaccine windows were included only in the second vaccine window and the denominator (follow-up time) was also truncated at the second vaccination. Thus, the incidence rate reflects the rate from 1st vaccination date to the earliest of: 90 days, end of follow-up or next vaccination date. A secondary analysis looked at the second and subsequent exposures to the vaccine.

4.6.2. Exploratory analysis: Self-controlled Case Series (SCCS)

The use of a Self-controlled Case Series (SCCS) design was explored [9, 10] as this signal involves a transient exposure for which risk windows can 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. [9, 10] Incidence rate ratios are derived comparing the rate of events during exposed periods of time with the rate during all other (unexposed) 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 [9, 10] (i.e., comparisons are made within individuals, therefore, individuals act as their own control).

For this study, we identified all patients with at least one incident diagnosis of pemphigoid or pemphigus 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 were included in the analysis.** Periods of follow-up with no exposure to COVID-19 vaccines were classified as "unexposed window". **Follow-up time was not censored at the occurrence of the event**, as later exposed and unexposed periods of time were included in the analysis. Risk periods were defined as 90-day periods after a vaccine exposure. **The length of the "unexposed" periods varied for each patient**.

Figure 1 illustrates the timeline and the unexposed and exposed windows. The null hypothesis was that the incidence of pemphigoid or pemphigus remains constant during the time periods and was not affected by exposure to Comirnaty, Spikevax or Vaxzevria vaccines.

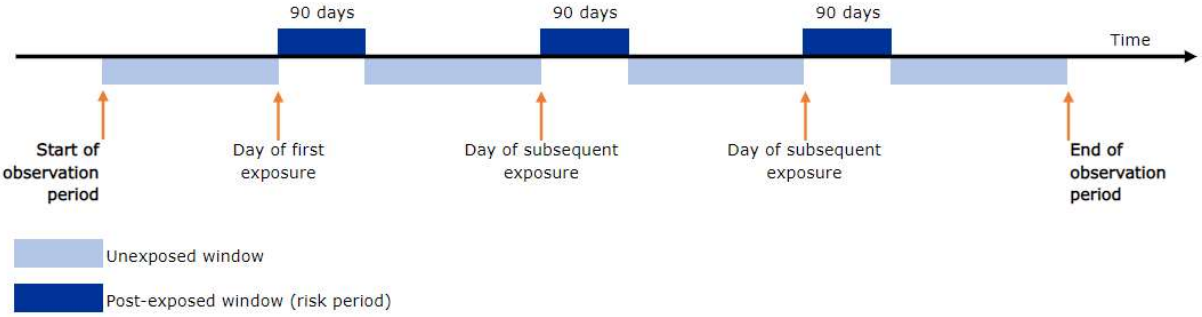

Figure 1. *Representation of (SSCS) study design: indicative single patient timeline.*

The key elements of this analysis are described below.

Data source: IMRD UK and THIN® Spain.

Study cohort: Patients vaccinated with Comirnaty, or Spikevax, or Vaxzevria **AND** with a diagnosis of pemphigoid or pemphigus from 2019 onwards. Of note, Spikevax was not included for IMRD UK analysis as there was insufficient exposure to this vaccine. In the UK, Spikevax was typically used only after exposure to the other vaccines. Follow-up time started 1-year (**observation time**) after first entry onto database.

Event definition: As defined in section 5.5 above. In this analysis, **repeated events were allowed** as per the SCCS design. 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, 8] 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) were 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 were coalesced into a single window.**
Subsequent post-vaccination "unexposed":	**from** n^{th} subsequent vaccination date + 90 days **to** n^{th} subsequent vaccination (or censored)

This analysis allows for multiple subsequent vaccination episodes to be incorporated (n^{th} vaccinations).

Pre- and post-initial vaccination "at risk" periods were evaluated separately to see if there is any evidence that the effect is not transient and combined if appropriate.

The underlying assumptions of this analysis are as follows:

- Given the relatively short study duration, potential confounding by age is unlikely to be an issue.
- Occurrence of the event is not expected to influence subsequent likelihood of vaccination (considering that there was no suggestion of COVID-19 vaccines being associated with increased risk of pemphigoid when the vaccine campaign was fully operational).
- 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 modelled event rates using a conditional Poisson regression to obtain a relative incidence rate. We compared event rates (n events / total follow-up time) in not-at-risk "unexposed" time windows to event rates in at risk "exposed" time windows (**primary model**). Additionally, we compared initial "at-risk" windows with subsequent "at-risk" windows. In a **second model**, we adjusted by age.

The period covered was from **01 January 2019 to 01 June 2022**.

4.6.3. Sensitivity analysis

For the **main analysis**, sensitivity analyses included:

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

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

- Using a **180-day risk window** (instead of 90 days).
- Using a **broad endpoint definition** of pemphigoid or pemphigus, including related conditions. See **Annex 2** for details.
- **Excluding patients with prior history** of pemphigoid or pemphigus at study entry.
- Excluding patients with prior history of pemphigoid or pemphigus at study entry AND **limiting outcome to the first (incident) event only.**
- Testing the 180-day **cut-off point** for **allowing repeated events** by **reducing to 90 days** and by **extending to 365 days**.
- **Excluding** patients **who did not survive** to end of study follow-up period (01Jun2022).
- Excluding patients exposed to medicines that are considered likely to be associated bullous disorders (i.e., drug-associated bullous pemphigoid (DABP) during the study period [3]: this is a potential time-dependant bias. **Annex 2** (**Table A5**) displays the list of medicines

considered in this analysis, which includes some commonly prescribed medicine such as aspirin and ibuprofen.

Analyses were carried out using SAS for IMRD UK and THIN® Spain.

4.7. Quality control

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

Standard operating procedures or 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 underwent at least one round review by an experienced reviewer, while the results from the statistical analysis were either reviewed or checked via double coding.

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

5. Results

In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database and <10 for THIN® Spain) 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.

Figure 2 illustrates the selection of the sample for the background incident rates, and the incident rates in exposed subjects.

5.1. Vaccine exposure

Table 1 shows the number of patients with a prescription for Comirnaty, Spikevax and Vaxzevria vaccines and the number of vaccinations recorded in both IMRD UK AND THIN® Spain databases. Figures are also stratified by sex, age group and year.

Roughly half of patients vaccinated with Comirnaty and Spikevax (47% and 52%, respectively) were ≥50 years of age in the **IMRD UK database**, whereas 63% of those vaccinated with Vaxzevria were in that age group. This suggests that the prescribing of Vaxzevria slightly favoured older age groups.

There was heterogeneity in the vaccine regiments used:

- 43.0% of vaccinated patients initially received two consecutive doses of **Comirnaty**. Of these, 54.3% subsequently had a third dose of Comirnaty and 34.2% had received no further vaccine by the end of follow-up. The remainder of patients received a vaccine other than Comirnaty (mostly Spikevax) for their third dose.
- 43.2% of vaccinated patients initially received two consecutive doses of **Vaxzevria**. Of these, 61.7% subsequently had Comirnaty as the third vaccine, and 15.6% had received no further

vaccine by the end of follow-up. The remainder of patients received a vaccine other than Comirnaty (mostly Spikevax) for their third dose.

- Spikevax was predominantly used as booster dose.

The median elapsed time between first dose and second dose was **77 days**.

In the **THIN® Spain database**, while 62% of patients vaccinated with Vaxzevria were ≥60 years of age, only 22-24% of vaccinated patients with Comirnaty and Spikevax were in that age group. This suggests that the prescribing of Vaxzevria markedly favoured older age groups, whereas Comirnaty and Spikevax markedly favoured younger age groups.

Similarly, there was heterogeneity in the vaccine regiments used:

- 59.3% of vaccinated patients initially received two consecutive doses of **Comirnaty**. Of these, 50.5% had received no further vaccine by the end of follow-up, 27.1% subsequently had a third dose of Spikevax and 22.3% subsequently had a third dose of Comirnaty.
- 13.7% of patients initially received two consecutive doses of **Spikevax**. Of these, 35.6% subsequently had a third dose of Spikevax, 63.2% had received no further vaccine by the end of follow-up. The remainder of patients subsequently had a third dose of vaccines other than Spikevax.
- 12.4% of vaccinated patients initially received two consecutive doses of **Vaxzevria**. Of these, 78.6% subsequently had a third dose of Spikevax, and 15.0% had received no further vaccine by the end of follow-up. The remainder of patients subsequently had a third dose of vaccine other than Spikevax.

  The median elapsed time between first dose and second dose was **21 days**.

5.2. Main results

5.2.1. Event rates in the general population

Table 2 shows the overall event rates for pemphigoid or pemphigus and event rates stratified by sex, age group and year of recorded diagnosis for the IMRD UK and THIN® Spain databases.

The overall incidence rate over the 10-year period in the **IMRD UK database** was 5.09 (95%CI: 4.75; 5.45) per 100,000 person-years. The incidence rate was slightly higher in female than male patients (5.46 [95%CI: 4.96;6.00] per 100,000 person-years and 4.73 [95%CI: 4.26;5.23] per 100,000 person-years, respectively) and it increased over time.

The overall incidence rate over the 6-year period in the **THIN® Spain database** was 12.31 (95%CI: 11.32; 13.37) per 100,000 person-years. There was no difference in the incidence rate between male and female patients and it remained steady from 2016 onwards.

In both databases, the incidence rates rose markedly with increasing age, particularly from 60 years onwards.

When including the codes covering bullous conditions more generally (**broad endpoint definition**), the overall incidence rates increased by 54-60% in IMRD UK and THIN® Spain databases, respectively (**Table 3**). Incidence rates stratified by age and year of diagnosis followed a similar pattern to that

found in each database when using the narrow endpoint definition. However, there was no difference in the incidence rates by sex in IMRD UK database, whereas female patients had a higher incidence rate than male patients in the THIN® Spain database (**Table 3**).

5.2.2. Standardised event rates in the general population

Standardised rates were estimated to allow comparisons of vaccines (see **section 5.6.1, iii**) which had been given to cohorts with different age structures.

The incidence rate of pemphigoid or pemphigus was twice as high in the THIN® Spain database than in the IMRD UK database (**Table 4**). In the **IMRD UK database,** the standardised event rates were slightly higher than the crude event rates in (**Table 4**) when using both the narrow and broad endpoint definitions.

5.2.3. Event rates among subjects exposed to COVID-19 vaccines

Table 5 shows standardised vaccine-exposed incidence rates of pemphigoid or pemphigus (**using narrow endpoint definition**) following first, second, and third dose in both the IMRD UK and THIN® Spain databases stratified by type of vaccine and vaccine window (either 90 or 180 days after receiving vaccination).

In the **IMRD UK database**, in the analysis looking at incidence rates of pemphigoid or pemphigus after **90 days** following first dose of Comirnaty vaccine (**Table 5**, first row), there were six events, however, the 95% confidence interval for the observed event rates overlapped with the expected event range in the population (**Table 4**, narrow endpoint definition). After **180 days** following first dose of Comirnaty (**Table 5**, fourth row), nine patients had a recorded diagnosis of pemphigoid or pemphigus, however, the 95% confidence interval for the observed event rates were within the expected event range in the population (**Table 4**, narrow endpoint definition). However, **after 90 and 180 days following the second dose of Comirnaty, the number of recorded events increased, and the incidence rates were higher-than-expected when compared to incidence rates in the general population** (**Table 4**, narrow endpoint definition).

For **Spikevax** vaccine, there was only a single case recorded after 180 days following the first dose and consequently the 95% confidence interval for the observed event rates overlapped with the expected event range in the population (**Table 5**). Of note, the follow-up time for Spikevax vaccine was much shorter than for the other vaccines (see Discussion).

For **Vaxzevria** vaccine, a **higher-than-expected incidence rate was only found in the 180-day window following the second dose** (**Table 5**).

Similar patterns were observed for the three vaccines **when including the codes covering bullous conditions more generally** (**broad endpoint definition**), but the numbers of events increased accordingly, particularly for Comirnaty and Vaxzevria vaccines (**Table 6**).

In the **THIN® Spain database**, although a few cases of pemphigoid or pemphigus were recorded after receiving the first and second dose of COVID-19 vaccines, particularly for Comirnaty, the 95% confidence interval for the observed event rates overlapped with the expected event range in the population when using either the narrow endpoint definition **(Table 5)** or the broad endpoint definition

(Table 6). In general, the confidence intervals of the incidence rates were relatively wide due to a limited number of follow-up years in each stratum.

In general, after receiving the **third dose,** limited number of cases were recorded of pemphigoid or pemphigus for Comirnaty vaccine, very few for Spikevax vaccine, and no cases for Vaxzevria vaccine **in both databases** (**Table 5** [narrow endpoint definition] and **Table 6** [broad endpoint definition]). It is worth noting that follow-up time was much shorter after the third dose.

5.2.4. Exploratory analysis: Self-controlled Case Series (SCCS)

Summary of results of the self-controlled case series (SCCS) analyses are shown in **Figure 3** for Comirnaty, **Figure 4** for Spikevax and **Figure 5** for Vaxzevria. Detailed results of main analyses for unexposed and post-exposed (combined and individual) window periods for each database and vaccine can be found in **Annex 3** (page 36). Details of results of additional and sensitivity analyses are available upon request.

<u>Comirnaty vaccine (Figure 3):</u>

- **Narrow endpoint definition:**

  In the IMRD UK database, 207 patients (median age: 83 years) who were exposed to Comirnaty vaccine and had a recorded diagnosis of pemphigoid or pemphigus were included in the SCCS analysis. These patients were followed-up for a total of 671 person-years and had 272 events recorded. In THIN® Spain, 350 patients (median age: 76.5 years) were exposed to Comirnaty vaccine and had a recorded diagnosis of pemphigoid or pemphigus. These patients were followed-up for a total of 1,156 person-years and had 516 events recorded.

  - **Post-exposed risk window: 90 days**

    - In **both databases**, there was no increase in the incidence rate ratio of pemphigoid or pemphigus in the 90-day risk window periods after vaccination in comparison to the unexposed window periods (**Figure 3,** first row on the top). Similar results were obtained when looking individually at subsequent exposed and unexposed windows (i.e., after receiving the first, second and third dose) in comparison to initial pre-exposure window (i.e., before first dose) (**Table A6** for IMRD UK, and **Table A22** for THIN® Spain).
    - Adjusting by age, excluding patients with previous history of pemphigoid or pemphigus, restricting the sample to first incident event only (and excluding patients with previous history of pemphigoid or pemphigus), allowing repeated events within 90 days (as opposed to 180 days) and excluding patients who did not survive to the end of study follow-up made no difference on the initial results (**Figure 3**). Allowing repeated events withing 365 days (as opposed to 180 days) showed a reduced incidence rate ratio in THIN® Spain (**Figure 3**), however, this was attenuated to 0.95 (95%CI: 0.66;1.37) after excluding patients with previous history of pemphigoid or pemphigus. Excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP) reduced substantially the sample size in both databases and consequently increased uncertainty, i.e., wider confidence intervals (which still cross the null value) (**Figure 3**). It is worth noting that the list of medicines considered in the analysis included some commonly prescribed drugs such as aspirin and ibuprofen (**Annex 2, Table A5**). Detailed

results for unexposed and post-exposed (combined and individual) window periods for these analyses are available upon request.

- **Post-exposed risk window: 180 days**
  - The incidence rate ratio of pemphigoid or pemphigus in the post-exposed window periods (all combined) was slightly higher than in the unexposed window periods (all combined) when extending the risk window period to 180 days after vaccination in IMRD UK (**Figure 3**). This **increase was more pronounced when excluding patients with prior history of pemphigoid or pemphigus in both databases** (IRR: 1.55 [95%CI: 1.13-2.14] in IMRD UK; and IRR: 1.34 [95%CI: 1.04-1.72] in THIN® Spain).

- **Broad endpoint definition:**

  In the IMRD UK database, 346 patients (median age: 81 years) who were exposed to Comirnaty vaccine and had recorded diagnosis of pemphigoid, pemphigus, or related conditions were included in the SCCS analysis. These patients were followed-up for a total of 1,113 person-years and had 437 events recorded. In THIN® Spain, 510 patients (median age: 73 years) were exposed to Comirnaty vaccine and had a recorded diagnosis of pemphigoid, pemphigus, or related conditions. These patients were followed-up for a total of 1,677 person-years and had 726 events recorded.

  - **Post-exposed risk window: 90 days and 180 days**
    - Overall, there was a slight increase in the incidence rate ratio of pemphigoid, pemphigus, or related conditions in the **90-** and **180- day** risk window following vaccination in comparison to the unexposed window in the IMRD UK database (**Figure 3**). However, this **increase was more pronounced in the 180- day risk window after excluding patients with prior history of pemphigoid, pemphigus, or related conditions in both databases** (IRR: 1.50 [95%CI: 1.19-1.90] in IMRD UK; and IRR: 1.23 [95%CI: 0.99-1.53] in THIN® Spain). This finding was consistent when assessing separately subsequent exposed and unexposed window periods in comparison to initial pre-exposure window, i.e., before first dose (**Table A13** for IMRD UK and **Table A29** for THIN® Spain).

Spikevax vaccine (Figure 4):

We present results only for THIN® Spain database. There were not enough cases of pemphigoid or pemphigus in patients exposed to Spikevax to conduct SCCS analysis in the IMRD UK database. Most patients in the IMRD UK database were exposed to either Comirnaty or Vaxzevria before receiving Spikevax vaccine. The latter was mostly used as a booster dose.

- **Narrow endpoint definition:**

  In THIN® Spain, 59 patients (median age: 76 years) who were both exposed to Spikevax vaccine and had recorded diagnosis of pemphigoid or pemphigus were included in the SCCS analysis. These patients were followed-up for a total of 197 person-years and had 74 events recorded.

  - **Post-exposed risk window: 90 days and 180 days**
    - Overall, the uncertainty of incidence rate ratios was high (wide confidence intervals) given the low number of cases of pemphigoid or pemphigus and the limited duration of the follow-up (person-years) (**Figure 4**).

- **Broad endpoint definition:**

  In THIN® Spain, 92 patients (median age: 57 years) who were both exposed to Spikevax vaccine and had recorded diagnosis of pemphigoid, pemphigus, or related conditions were included in the SCCS analysis. These patients were followed-up for a total of 304 person-years and had 114 events recorded.

  - **Post-exposed risk window: 90 days and 180 days**

    - Similarly, the uncertainty of incidence rate ratios was high (wide confidence intervals) given the low number of cases of pemphigoid or pemphigus and the limited duration of the follow-up (person-years) (**Figure 4**). However, **the incidence rate ratio of pemphigoid, pemphigus, or related conditions was higher in the 90- and 180- day risk window following vaccination in comparison to unexposed window, particularly after excluding patients with prior history of pemphigoid or pemphigus** (IRR: 1.76 [95%CI: 1.13-2.76] in the 90-day window, and IRR: 1.64 [95%CI: 1.10-2.45] in the 180-day window). These findings were consistent when assessing separately subsequent exposed and unexposed window periods in comparison to initial pre-exposure window, i.e., before first dose (**Table A35** and **Table A37**).

Vaxzevria vaccine (Figure 5):

- **Narrow endpoint definition:**

  In the IMRD UK database, 198 patients (median age: 75 years) who were exposed to Vaxzevria vaccine and had recorded event of pemphigoid or pemphigus were included in the SCCS analysis. These patients were followed-up for a total of 557 person-years and had 257 events recorded. In THIN® Spain, 45 patients (median age: 63 years) who were exposed to Vaxzevria vaccine and had recorded event of pemphigoid or pemphigus were included in the SCCS analysis. These patients were followed-up for a total of 134 person-years and had 67 events recorded.

  - **Post-exposed risk window: 90 days and 180 days**

    - In IMRD UK, **the incidence rate ratio of pemphigoid, pemphigus, or related conditions was higher in 180- day risk window following vaccination in comparison to unexposed window** (IRR: 1.39 [95%CI: 1.01-1.92]) **after excluding patients with prior history of pemphigoid or pemphigus** (**Figure 5** and **Table A17**).

    - In THIN® Spain, the uncertainty of incidence rate ratios was high (wide confidence intervals) given the low number of cases of pemphigoid or pemphigus and the limited duration of the follow-up (person-years).

- **Broad endpoint definition:**

  In the IMRD UK database, 319 patients (median age: 74 years) who were exposed to Vaxzevria vaccine and had recorded event of pemphigoid, pemphigus, or related conditions were included in the SCCS analysis. These patients were followed-up for a total of 895 person-years and had 407 events recorded. In THIN® Spain, 86 patients (median age: 62.5 years) who were exposed to Vaxzevria vaccine and had recorded event of pemphigoid or pemphigus were included in the SCCS analysis. These patients were followed-up for a total of 258 person-years and had 115 events recorded.

- **Post-exposed risk window: 90 days and 180 days**
    - In IMRD UK, **the incidence rate of pemphigoid, pemphigus, or related conditions was higher in 180- day risk window following vaccination in comparison to unexposed window** (IRR: 1.41 [95%CI: 1.10-1.80]) **after excluding patients with prior history of pemphigoid or pemphigus** (**Figure 5** and **Table A21**).
    - In THIN® Spain, the uncertainty of incidence rate ratios was high (wide confidence intervals) given the low number of cases of pemphigoid or pemphigus and the limited duration of the follow-up (person-years).

N.B.: Details of results of the following additional and sensitivity analyses are available upon request: adjusting by age, restricting the sample to first incident event only and excluding patients with previous history of pemphigoid or pemphigus, allowing repeated events within 90 days (as opposed to 180 days), allowing repeated events withing 365 days (as opposed to 180 days), excluding patients who did not survive to the end of study follow-up, excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP).

6. Discussion and conclusions

6.1. Key messages

- While Comirnaty and Vaxzevria were the most often vaccines prescribed in IMRD UK database, Comirnaty and Spikevax were the most prescribed in THIN® Spain database, which reflects the policy of COVID-19 vaccination programme in each country. For instance, Comirnaty and Vaxzevria were mostly used as primary series vaccinations in the UK, while Spikevax was used mostly as a booster dose.
- There was heterogeneity in the vaccine regiments used in both databases, including use of homologous and heterologous booster vaccinations. In addition, the timing of vaccination schedules was very different across databases. In Spain, the COVID-19 vaccine programme typically allowed three weeks between the first and second doses, whilst the UK policy was to allow 2-3 months between them.
- The use of COVID-19 vaccines also differed by age group. For instance, the prescribing of Vaxzevria vaccine was slightly more often among older groups than younger groups in the IMRD UK database. The prescribing of Comirnaty was markedly common among younger groups and accordingly the prescribing of Vaxzevria was more often among older groups in the THIN® Spain database.
- The background incidence rates of pemphigoid or pemphigus from IMRD UK were similar to another UK-based study from 2008 which reported incidences of bullous pemphigoid and pemphigus vulgaris of 4.3 (95% confidence interval 4.0 to 4.6) and 0.7 (0.6 to 0.8) per 100 000 person years, respectively (13).
- The background incidence rate of pemphigoid or pemphigus was twice as high in the THIN® Spain database than in the IMRD UK database. This might reflect differences in the populations of the underlying healthcare system. For IMRD UK, patients included are those registered with

a GP practice; however, such subjects might not be active member of the healthcare seeking population. For THIN® Spain, subjects are only included in analyses if they have two or more interactions with their healthcare provider, so there might be underrepresentation of relatively healthy subjects. Differences in incidence rates might also reflect application of different diagnostic criteria or different coding practices. As previously stated, bullous pemphigoid may be characterised by an initial pre-bullous phase with nonspecific symptoms which may last for several weeks or months. Diagnosis then involves referral to secondary care and requires confirmation by serology/histology. Thus, time to diagnosis may take many weeks or months. Differences in the diagnosis/referral patterns or awareness of BP in the medical communities might contribute to geographic variations in disease estimates. Alternatively, there might be a true difference in the burden of the disease between the two populations in terms of ethnic differences. For example, there are reports of a predisposition to pemphigus vulgaris in individuals of Mediterranean ancestry (14).

- There was a clear pattern of increase in the incidence of pemphigoid or pemphigus with increasing age. Subjects aged 80 or older had the highest incidence of pemphigoid or pemphigus in comparison with other age groups in both databases. This finding is consistent with previous studies (3, 11, 13). It has been suggested that the rise in the use of certain drugs (e.g., antidiabetic drug dipeptidyl peptidase-4 inhibitor) and in the prevalence of certain diseases (e.g., dementia and Parkinson's) are associated with the increased incidence rate of bullous pemphigoid in the elderly population (3, 11).
- Post-vaccination standardised incidence rates of pemphigoid or pemphigus were higher than the background incidence rates during the **90-day and the 180-day periods after receiving the second dose of Comirnaty,** using either the narrow or the broad endpoint definition in the **IMRD UK database**.
- Post-vaccination standardised incidence rate of pemphigoid or pemphigus was higher than the background incidence rates during the **180-day period after receiving the second dose of Vaxzevria** using the narrow endpoint definition. Additionally, post-vaccination incidence rates were higher than the background incidence rates during the 90-day and the 180-day periods after receiving the second dose of Vaxzevria using the broad endpoint definition in the **IMRD UK database**.
- There were very few cases recorded of pemphigoid or pemphigus after exposure to Spikevax vaccine in both databases. It is worth noting that the follow-up time for Spikevax in the IMRD UK database was markedly shorter than for other vaccines. This could be explained by the UK policy for its COVID-19 vaccination programme in which Spikevax was typically used as a booster rather than as a primary series vaccination.
- No difference between the background and post-vaccination incidence rates was found in the THIN® Spain database (see bullet point 4 above).
- Findings from the comparison between background and post-vaccination incidence rates were not consistent across databases (i.e., IMRD UK and THIN® Spain). This might be partly explained by the difference in the vaccine scheme between the two countries. While the median elapsed time between the first and the second dose in the UK was nearly three months, the median elapsed time in Spain was only three weeks. Therefore, time-to-onset of disease and time to diagnosis might have played a role in the different results between databases. In addition, the use of different diagnosis criteria might contribute to these differences across countries (see bullet point 4).

- The **SCCS analyses suggest an increase in the incidence rate of pemphigoid or pemphigus in the 180-day risk period following vaccination with Comirnaty, Spikevax or Vaxzevria.** There was evidence of consistency when applying the broad endpoint definition and excluding patients with prior history of pemphigoid or pemphigus. Excluding patients with a prior history suggest that observed events are truly incident (new) events.
- Results based on the **broad endpoint definition** and longer risk window period (**180-day**) were consistent across:
    - The two types of analyses, (i.e., the comparison between **background and post-vaccination incidence rates and the SCCS analysis)** in the IMRD UK database.
    - The **three vaccines** (Comirnaty, Spikevax and Vaxzevria) and the **two databases** in the **SCCS analyses** (except for Vaxzevria in THIN® Spain, where there was a small number of cases and limited follow-up period), **after excluding patients with previous history of pemphigoid or pemphigus**.
- Further studies using other data sources to replicate and confirm our findings would strengthen the available evidence, particularly analysis based on SCCS design. In addition, sensitivity analysis including additional follow-up periods should be explored.

6.2. 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 for research purposes.

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 was not possible. For this reason, we have explored the approach of using the SCCS study design.

Diagnostic coding for pemphigoid or pemphigus 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. Persson *et al* [11] 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. We assessed narrow and broad definitions in the analyses to account for uncertainties around potential misclassification. Overall, estimates were consistent (i.e., there were no substantial differences) when using both endpoint definitions across the different analyses.

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. Additionally, given that the SCCS approach is susceptible to time-dependant confounding, we have tested this scenario in the case of co-prescribed medicines that are known to be associated with pemphigoid or pemphigus. However, it is possible that some infections such as COVID-19 might itself trigger these conditions [12]. This has not been accounted for in the analysis.

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Tables and figures

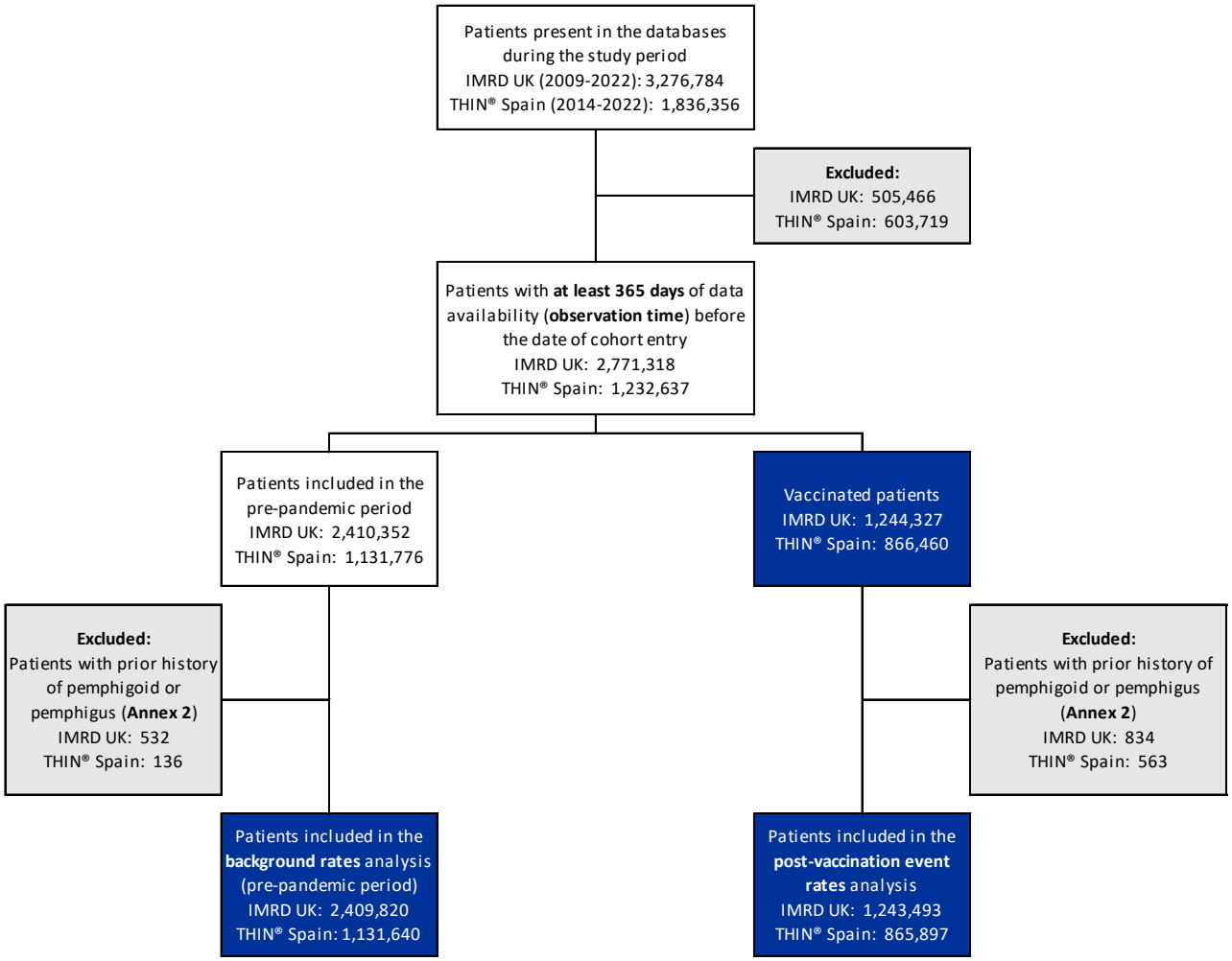

Figure 2. *Flowchart of the selection of the sample for the analysis of background incidence rates and post-vaccination incidence rates.*

Note: Figures for patients included in the background rates and rates among exposed patients are slightly higher when using the broad endpoint definition.

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

	IMRD EMIS UK						THIN® Spain					
	Comirnaty		Spikevax		Vaxzevria		Comirnaty		Spikevax		Vaxzevria	
	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations
Overall	912,946	1,716,880	289,793	332,987	515,345	1,009,691	591,572	1,233,886	398,575	555,792	115,227	222,782
Sex												
Female	476,524	912,165	143,529	162,970	261,081	511,817	285,130	589,255	194,578	273,106	52,258	101,292
Male	436,422	804,715	146,264	170,017	254,264	497,874	306,442	644,631	203,997	282,686	62,969	121,490
Age at first use (years)												
<30	228,955	438,389	41,174	55,667	27,632	53,117	167,488	310,957	54,385	85,827	5,833	10,795
30-39	146,832	302,958	48,621	64,167	46,570	90,174	83,250	160,825	63,618	101,949	7,540	13,963
40-49	111,070	183,346	49,476	58,820	118,082	230,332	115,964	230,707	86,858	109,737	9,931	18,328
50-54	64,073	100,878	26,287	26,789	73,823	145,226	50,862	102,181	49,361	67,074	8,083	14,905
55-59	65,695	106,488	26,015	26,424	68,206	134,475	41,170	84,374	46,284	64,353	10,445	20,316
60-64	60,341	100,188	20,229	20,535	54,624	107,832	10,510	18,972	43,882	46,123	43,333	84,914
65-69	58,390	99,751	10,808	11,021	42,432	84,000	14,012	27,944	37,283	41,370	30,026	59,522
70-74	61,767	109,233	9,263	9,579	41,904	82,909	37,504	97,330	7,494	17,487	19	21
75-79	50,534	110,250	27,095	28,153	23,451	46,195	29,971	85,524	3,248	6,940	12	12
80-84	34,955	91,427	16,231	16,703	8,269	15,895	18,953	53,963	3,597	8,929	<10	<10
≥85	30,334	73,972	14,594	15,129	10,352	19,536	21,888	61,109	2,565	6,003	<10	<10
Year												
2020	21,949	22,559	N/A	N/A	148	261	2,625	6,539	N/A	N/A	N/A	N/A
2021	821,635	1,489,865	188,353	223,248	515,125	1,008,818	557,596	1,178,830	243,298	399,430	115,208	222,763
2022	69,362	204,456	101,440	109,739	72	612	31,351	48,517	155,277	156,362	19	19

N/A = not applicable; 95% CI: 95% Confidence intervals

Table 2. *Incidence rates of new onset pemphigoid and pemphigus* ***[using narrow endpoint definition]*** *in the general population per 100,000 person-years of follow-up between 2009 and 2019: overall and stratified by sex, age groups and year of diagnosis*

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	816	16,023,274	5.09 (4.75-5.45)	569	4,620,989	12.31 (11.32-13.37)
Sex						
Female	436	7,986,654	5.46 (4.96-6.00)	294	2,418,717	12.16 (10.81-13.63)
Male	380	8,036,620	4.73 (4.26-5.23)	275	2,202,272	12.49 (11.05-14.05)
Age (in years)						
<30	32	5,529,974	0.58 (0.40-0.82)	59	1,361,800	4.33 (3.30-5.59)
30-39	25	2,291,899	1.09 (0.71-1.61)	26	677,101	3.84 (2.51-5.63)
40-49	40	2,463,617	1.62 (1.16-2.21)	31	761,599	4.07 (2.77-5.78)
50-54	24	1,160,138	2.07 (1.33-3.08)	28	343,439	8.15 (5.42-11.78)
55-59	36	995,435	3.62 (2.53-5.01)	18	309,345	5.82 (3.45-9.20)
60-64	46	886,920	5.19 (3.80-6.92)	29	273,842	10.59 (7.09-15.21)
65-69	80	805,656	9.93 (7.87-12.36)	44	252,784	17.41 (12.65-23.37)
70-74	75	663,324	11.31 (8.89-14.17)	61	218,830	27.88 (21.32-35.81)
75-79	127	496,354	25.59 (21.33-30.44)	66	160,845	41.03 (31.74-52.20)
80-84	148	352,093	42.03 (35.54-49.38)	92	133,182	69.08 (55.69-84.72)
≥85	183	377,863	48.43 (41.67-55.98)	115	128,222	89.69 (74.05-107.7)
Year						
2009	42	1,000,816	4.20 (3.02-5.67)	N/A	N/A	N/A
2010	33	1,067,129	3.09 (2.13-4.34)	N/A	N/A	N/A
2011	45	1,155,309	3.90 (2.84-5.21)	N/A	N/A	N/A
2012	53	1,266,985	4.18 (3.13-5.47)	N/A	N/A	N/A
2013	70	1,382,939	5.06 (3.95-6.40)	N/A	N/A	N/A
2014	79	1,504,435	5.25 (4.16-6.54)	43	170,516	25.22 (18.25-33.97)
2015	93	1,611,293	5.77 (4.66-7.07)	105	668,868	15.70 (12.84-19.00)
2016	89	1,681,820	5.29 (4.25-6.51)	101	866,995	11.65 (9.49-14.16)
2017	111	1,742,831	6.37 (5.24-7.67)	89	935,154	9.52 (7.64-11.71)
2018	95	1,788,904	5.31 (4.30-6.49)	108	976,379	11.06 (9.07-13.35)
2019	106	1,820,813	5.82 (4.77-7.04)	123	1,003,078	12.26 (10.19-14.63)

N/A = not applicable; 95% CI: 95% Confidence intervals

Table 3. *Incidence rates of new onset pemphigoid and pemphigus* ***[using broad endpoint definition]*** *in the general population per 100,000 person-years of follow-up between 2009 and 2019: overall and stratified by sex, age groups and year of diagnosis*

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	1,254	16,013,347	7.83 (7.40-8.28)	910	4,619,887	19.70 (18.44-21.02)
Sex						
Female	617	7,981,459	7.73 (7.13-8.37)	516	2,418,011	21.34 (19.54-23.26)
Male	637	8,031,888	7.93 (7.33-8.57)	394	2,201,875	17.89 (16.17-19.75)
Age (in years)						
<30	102	5,528,493	1.84 (1.50-2.24)	138	1,361,535	10.14 (8.52-11.97)
30-39	57	2,290,784	2.49 (1.88-3.22)	70	676,978	10.34 (8.06-13.06)
40-49	76	2,462,239	3.09 (2.43-3.86)	80	761,439	10.51 (8.33-13.08)
50-54	43	1,159,315	3.71 (2.68-5.00)	47	343,386	13.69 (10.06-18.20)
55-59	60	994,627	6.03 (4.60-7.76)	56	309,257	18.11 (13.68-23.51)
60-64	82	886,062	9.25 (7.36-11.49)	52	273,755	19.00 (14.19-24.91)
65-69	122	804,808	15.16 (12.59-18.10)	67	252,718	26.51 (20.55-33.67)
70-74	120	662,523	18.11 (15.02-21.66)	78	218,727	35.66 (28.19-44.51)
75-79	176	495,654	35.51 (30.46-41.16)	83	160,776	51.62 (41.12-64.00)
80-84	192	351,509	54.62 (47.17-62.92)	102	133,137	76.61 (62.47-93.00)
≥85	224	377,335	59.36 (51.84-67.67)	137	128,179	106.9 (89.73-126.4)
Year						
2009	64	1,000,142	6.40 (4.93-8.17)	N/A	N/A	N/A
2010	58	1,066,414	5.44 (4.13-7.03)	N/A	N/A	N/A
2011	78	1,154,549	6.76 (5.34-8.43)	N/A	N/A	N/A
2012	85	1,266,169	6.71 (5.36-8.30)	N/A	N/A	N/A
2013	97	1,382,073	7.02 (5.69-8.56)	N/A	N/A	N/A
2014	116	1,503,513	7.72 (6.38-9.25)	60	170,499	35.19 (26.85-45.30)
2015	135	1,610,320	8.38 (7.03-9.92)	145	668,781	21.68 (18.30-25.51)
2016	146	1,680,801	8.69 (7.33-10.22)	159	866,852	18.34 (15.60-21.43)
2017	164	1,741,794	9.42 (8.03-10.97)	161	934,942	17.22 (14.66-20.10)
2018	142	1,787,844	7.94 (6.69-9.36)	181	976,095	18.54 (15.94-21.45)
2019	169	1,819,728	9.29 (7.94-10.80)	204	1,002,717	20.34 (17.65-23.34)

N/A = not applicable; 95% CI: 95% Confidence intervals

Table 4. *Non-standardised and standardised incidence rates of new onset pemphigoid or pemphigus in the general population per 100,000 person-years of follow-up*

Database	Endpoint definition	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	Narrow	816	16,023,274	5.09 (4.75-5.45)	**6.12 (5.70-6.55)**
	Broad	1,254	16,013,347	7.83 (7.40-8.28)	**9.16 (8.65-9.68)**
THIN® Spain	Narrow	569	4,620,989	12.31 (11.32-13.37)	**12.88 (11.84-13.97)**
	Broad	910	4,619,887	19.70 (18.44-21.02)	**20.29 (18.99-21.65)**

95% CI: 95% Confidence intervals

Table 5. *Standardised incidence rates of new onset pemphigoid or pemphigus* ***[using narrow endpoint definition]*** *per 100,000 years of follow-up following exposure to COVID-19 vaccines*

Database	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	6	113,244	5.32 (1.82-11.18)	16	118,999	**12.93 (7.05-20.97)**	<6	-	1.69 (0.33-4.54)
	Spikevax		0	9,259	0.00 (.-.)	0	7,563	0.00 (.-.)	0	2,232	0.00 (.-.)
	Vaxzevria		<6	-	5.75 (1.38-13.48)	12	121,122	11.41 (5.44-19.98)	0	354	0.00 (.-.)
	Comirnaty	**180-day**	9	133,042	7.37 (3.12-13.84)	29	215,862	**10.84 (7.00-15.68)**	12	122,654	4.41 (2.01-7.85)
	Spikevax		<6	-	3.66 (0.09-17.12)	0	12,939	0.00 (.-.)	0	3,717	0.00 (.-.)
	Vaxzevria		7	109,241	6.94 (2.28-14.44)	25	238,267	**12.11 (7.43-18.10)**	0	643	0.00 (.-.)
THIN® Spain	Comirnaty	90-day	<10	-	20.28 (9.18-37.14)	16	113,759	10.65 (5.93-17.09)	<10	-	3.76 (1.35-7.82)
	Spikevax		<10	-	23.37 (0.00-85.88)	<10	-	8.98 (1.08-28.83)	<10	-	20.45 (4.21-54.59)
	Vaxzevria		<10	-	8.90 (0.00-34.76)	<10	-	1.28 (0.14-4.13)	0	7	0.00 (.-.)
	Comirnaty	**180-day**	<10	-	18.01 (8.10-33.08)	36	218,673	12.81 (8.79-17.75)	20	48,432	7.19 (4.34-10.94)
	Spikevax		<10	-	25.18 (0.00-81.75)	<10	-	18.99 (7.11-38.14)	<10	-	17.14 (5.54-37.62)
	Vaxzevria		<10	-	7.98 (0.00-31.04)	<10	-	1.14 (0.22-3.06)	0	13	0.00 (.-.)

* **N.B.:** Events that occur within both the first and second vaccine windows were included only in the second vaccine window and the denominator (follow-up time) was also truncated at the second vaccination. Thus, the incidence rate is the rate from 1st vaccination date to the earliest of: 90 days, end of follow-up or next vaccination date.

95% CI: 95% Confidence intervals

Table 6. *Standardised incidence rates of new onset pemphigoid or pemphigus* ***[using broad endpoint definition]*** *per 100,000 years of follow-up following exposure to COVID-19 vaccines*

Database	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	12	113,147	9.39 (4.67-16.16)	20	118,890	**15.91 (9.34-24.58)**	10	67,025	8.39 (2.92-16.54)
	Spikevax		0	9,255	0.00 (.-.)	0	7,560	0.00 (.-.)	0	2,231	0.00 (.-.)
	Vaxzevria		12	104,205	10.85 (4.90-19.40)	21	121,000	**16.53 (9.61-25.60)**	0	352	0.00 (.-.)
	Comirnaty	**180-day**	18	132,935	12.83 (7.30-20.25)	40	215,652	**14.82 (10.30-20.33)**	25	122,500	10.61 (6.19-16.27)
	Spikevax		<6	-	19.68 (0.00-71.00)	0	12,934	0.00 (.-.)	0	3,715	0.00 (.-.)
	Vaxzevria		15	109,136	12.30 (6.20-20.72)	43	238,022	**19.11 (12.56-27.01)**	0	641	0.00 (.-.)
THIN® Spain	Comirnaty	90-day	11	43,207	24.32 (12.05-42.22)	30	113,697	22.75 (14.96-32.51)	<10	-	3.77 (1.35-7.83)
	Spikevax		<10	-	81.48 (26.22-170.5)	<10	-	8.98 (1.08-28.83)	<10	-	140.7 (0.00-388.2)
	Vaxzevria		<10	-	11.93 (0.00-37.41)	<10	-	1.87 (0.37-5.02)	0	7	0.00 (.-.)
	Comirnaty	**180-day**	11	51,761	21.30 (10.47-37.10)	56	218,553	21.38 (15.81-27.96)	20	48,391	7.19 (4.34-10.95)
	Spikevax		<10	-	74.87 (23.15-155.6)	<10	-	22.16 (9.35-41.63)	<10	-	106.7 (0.00-287.7)
	Vaxzevria		<10	-	14.79 (1.92-39.17)	<10	-	2.20 (0.79-4.57)	0	13	0.00 (.-.)

* **N.B.:** Events that occur within both the first and second vaccine windows were included only in the second vaccine window and the denominator (follow-up time) was also truncated at the second vaccination. Thus, the incidence rate is the rate from 1st vaccination date to the earliest of: 90 days, end of follow-up or next vaccination date.

95% CI: 95% Confidence intervals

Summary of results of the self-controlled case series (SCCS) analysis:

N.B: Detailed results of main analyses for unexposed and post-exposed (combined and individual) window periods for each database and vaccine can be found in **Annex 3.** Details of results of additional and sensitivity analyses are available upon request (i.e., adjusting by age, restricting the sample to first incident event only and excluding patients with previous history of pemphigoid or pemphigus, allowing repeated events within 90 days (as opposed to 180 days), allowing repeated events withing 365 days (as opposed to 180 days), excluding patients who did not survive to the end of study follow-up, excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP)).

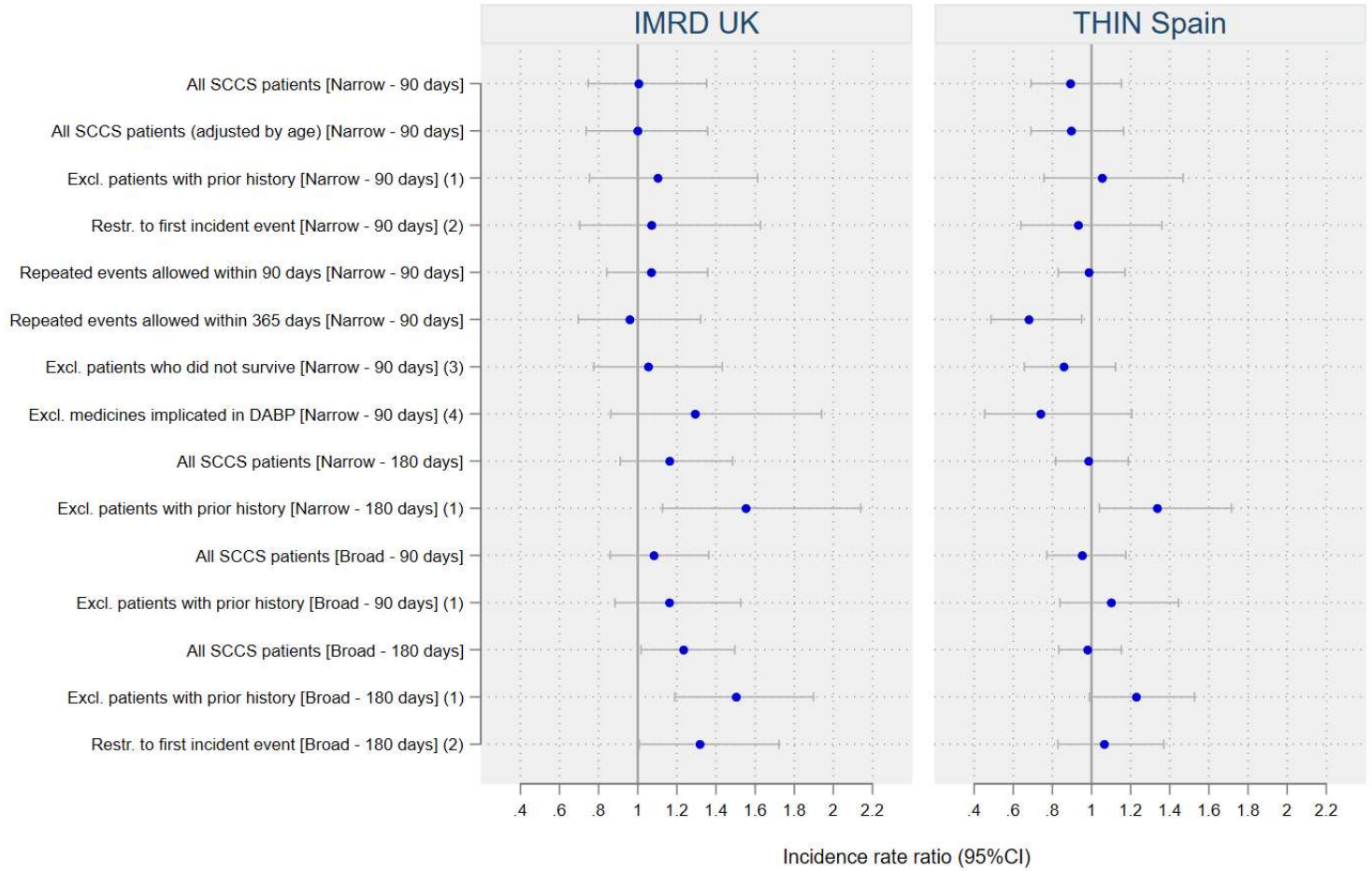

Figure 3. Comirnaty vaccine: *Incidence rate ratio (IRR) (and 95% confidence interval (95% CI)) for pemphigoid or pemphigus in the post-exposed window periods [all combined] in comparison to the unexposed window periods [all combined] (reference category). Blue dots illustrate IRRs and horizontal grey lines represent 95% CIs. X-axis uses an arithmetic scale.*

Notes: *Unless differently indicated, repeated events were allowed within a 180 day-period; Narrow: narrow endpoint definition; Broad: broad endpoint definition; 90 days: post-exposed (risk) window within 90 days following vaccination; 180 days: post-exposed (risk) window within 180 days following vaccination; (1) excluding patients with prior history of pemphigoid or pemphigus; (2) restriction to first incident event only and excluding patients with prior history of pemphigoid or pemphigus; (3) excluding patients who did not survive to the end of the study follow-up period; (4) excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP).*

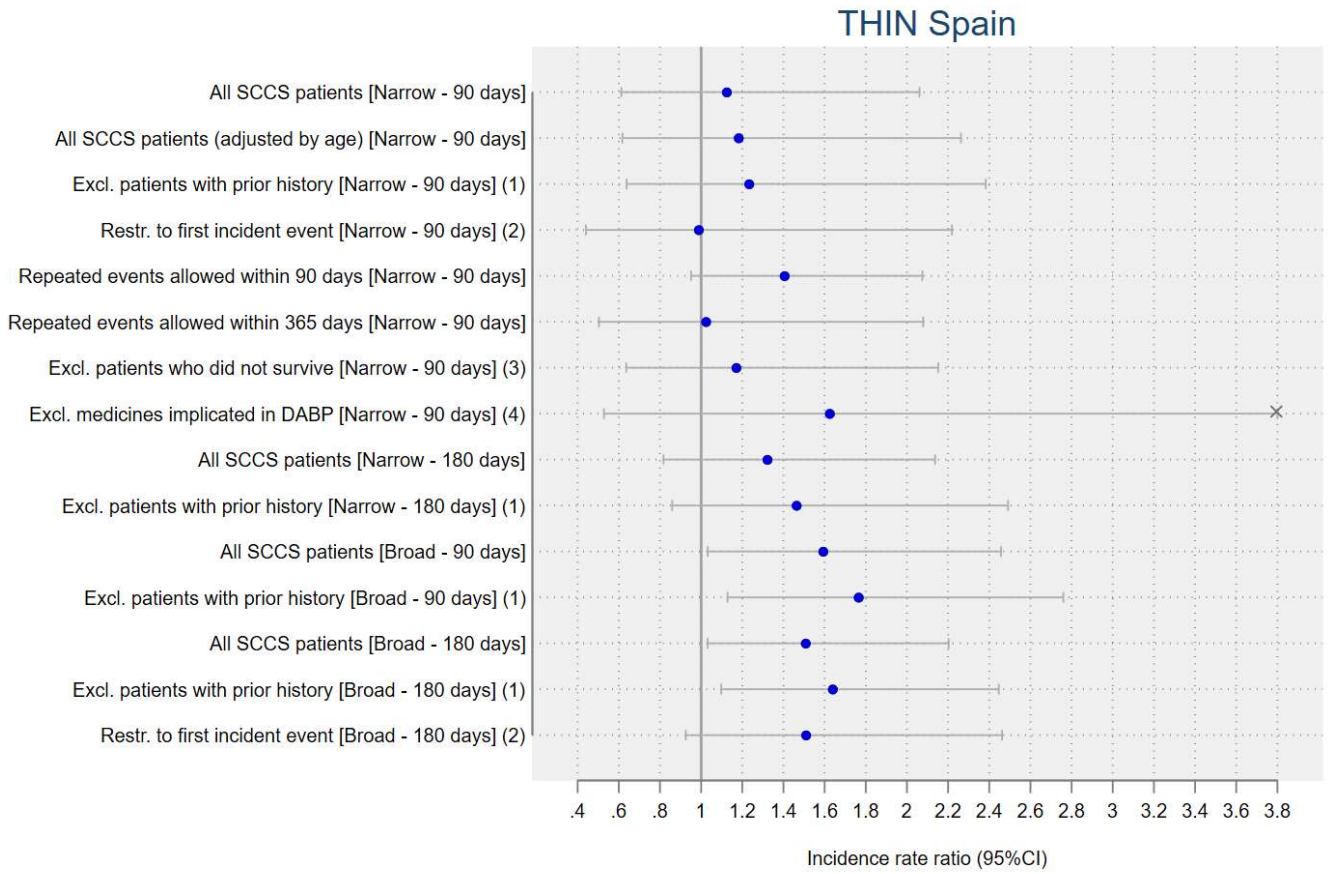

Figure 4. Spikevax vaccine: *Incidence rate ratio (IRR) (and 95% confidence interval (95% CI)) for pemphigoid or pemphigus in the post-exposed window periods [all combined] in comparison to the unexposed window periods [all combined] (reference category). Blue dots illustrate IRRs, horizontal grey lines represent 95% Cis, and "x" indicates that the upper 95% CI was truncated (actual value 5.0). X-axis uses an arithmetic scale. Results are only shown for THIN® Spain. There was not enough follow-up time for Spikevax vaccine to conduct SCCS in the IMRD UK.*

Notes: *Unless differently indicated, repeated events were allowed within a 180 day-period; Narrow: narrow endpoint definition; Broad: broad endpoint definition; 90 days: post-exposed (risk) window within 90 days following vaccination; 180 days: post-exposed (risk) window within 180 days following vaccination; (1) excluding patients with prior history of pemphigoid or pemphigus; (2) restriction to first incident event only and excluding patients with prior history of pemphigoid or pemphigus; (3) excluding patients who did not survive to the end of the study follow-up period; (4) excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP).*

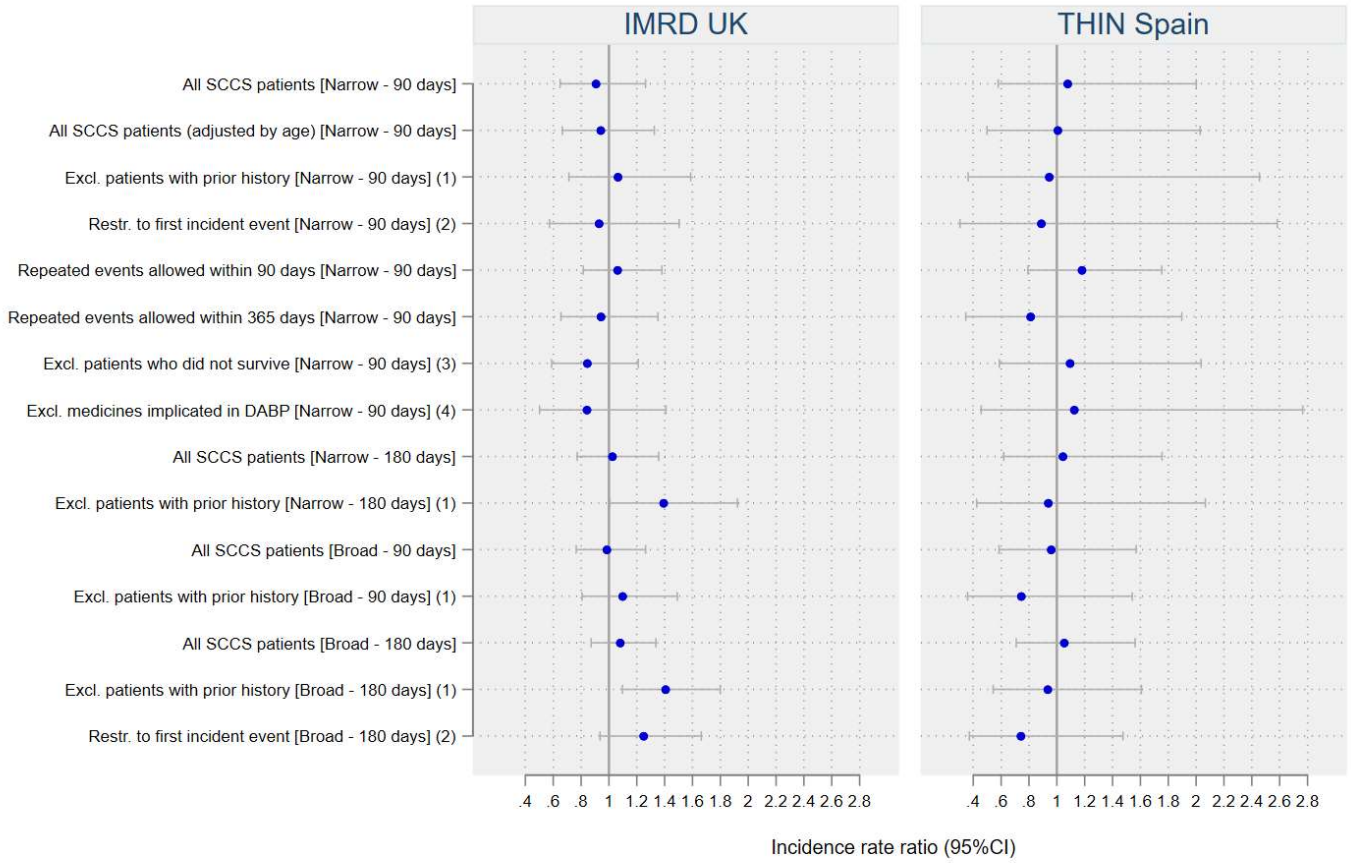

Figure 5. Vaxzevria vaccine: *Incidence rate ratio (IRR) (and 95% confidence interval (95% CI)) for pemphigoid or pemphigus in the post-exposed window periods [all combined] in comparison to the unexposed window periods [all combined] (reference category). Blue dots illustrate IRRs and horizontal grey lines represent 95% CIs. X-axis uses an arithmetic scale.*
Notes: *Unless differently indicated, repeated events were allowed within a 180 day-period; Narrow: narrow endpoint definition; Broad: broad endpoint definition; 90 days: post-exposed (risk) window within 90 days following vaccination; 180 days: post-exposed (risk) window within 180 days following vaccination; (1) excluding patients with prior history of pemphigoid or pemphigus; (2) restriction to first incident event only and excluding patients with prior history of pemphigoid or pemphigus; (3) excluding patients who did not survive to the end of the study follow-up period; (4) excluding patients exposed to medicines implicated in drug-associated bullous pemphigoid (DABP).*

Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) EMIS 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 paediatricians & 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. Its data are 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 eight and nine 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 (8%)
M1450	Bullous pemphigoid (54%)
M145	Pemphigoid (23%)
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 (5%)
Broad endpoint case definition covering bullous conditions more generally (codes below were included *in addition* to those above for the broad definition)	
PH331-1	Benign familial chronic pemphigus
M141-1	Sneddon - Wilkinson disease
M140	Dermatitis herpetiformis (adds quite a few cases)
M14	Bullous dermatoses (adds quite a few cases)
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 (adds quite a few cases)
^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) (0.3%)
FUES.CIE9.694.4	PEMPHIGUS (L10.0) (40%)
FUES.CIE9.694.5	PEMPHIGOID (L12.0) (58%)
FUES.CIE9.694.6	BENIGN MUCOUS MEMBRANE PEMPHIGOID (L12.1) (<1%)
FUES.CIE9.694.60	BENIGN MUCOUS MEMBRANE PEMPHIGOID - WITHOUT OCULAR INVOLVEMENT (L12.1) (<1%)
FUES.CIE9.694.61	BENIGN MUCOUS MEMBRANE PEMPHIGOID - WITH OCULAR INVOLVEMENT (L12.1) (<1%)
Broad endpoint case definition covering bullous conditions more generally (codes below were included *in addition* to those above for the broad definition)	
FUES.CIE9.694	BULLOUS DERMATOSES (L13.9)
FUES.CIE9.694.0	DERMATITIS HERPETIFORMIS (L13.0) (adds quite a few cases)
FUES.CIE9.694.1	SUBCORNEAL PUSTULAR DERMATOSIS (L13.1) (adds a few cases)
FUES.CIE9.694.8	OTHER SPECIFIED BULLOUS DERMATOSES (L13.8)
FUES.CIE9.694.9	UNSPECIFIED BULLOUS DERMATOSES (L13.9) (adds quite a few cases)
Related codes not included	
FUES.CIE9.694.3	IMPETIGO HERPETIFORMIS (L40.1)

Table A5. *List of medicines implicated in drug-associated bullous pemphigoid (DABP)*

Medicines likely associated with DABP [3]
Alogliptin
Anagliptin
Aspirin
Biostim
Penicillamine
Enalapril
Erlotinib
Etanercept
Everolimus
Furosemide
Ibuprofen
Levofloxacin
Linagliptin
Nivolumab
Pembrolizumab
Phenacetin
Psoralen
Rifampicin
Serratiopeptidase
Sirolimus
Sitagliptin
Teneligliptin
Tetanus toxoid
Tiobutarit
Vildagliptin

Annex 3 – Detailed results of the Self-controlled case series (SCCS) analysis

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 90 days

Table A6. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (narrow endpoint definition, 90-day risk window period, all patients n=207)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	216	535	0.40 (0.35-0.46)	Reference
90-day post-exposed window periods (all combined)	56	136	0.41 (0.31-0.53)	1.00 (0.75-1.35)
Individual window periods				
Initial pre-exposure window	166	431	0.39 (0.33-0.45)	Reference
1st exposed window	38	84	0.45 (0.32-0.62)	1.18 (0.83-1.66)
1st post-vaccination unexposed window	32	64	0.50 (0.34-0.70)	1.34 (0.92-1.93)
Subsequent exposed windows	18	53	0.34 (0.20-0.54)	0.88 (0.55-1.40)
Subsequent unexposed windows	18	40	0.45 (0.27-0.72)	1.23 (0.75-1.99)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 90 days

Table A7. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (narrow endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=130)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	122	340	0.36 (0.30-0.43)	Reference
90-day post-exposed window periods (all combined)	33	83	0.40 (0.27-0.56)	1.10 (0.75-1.61)
Individual window periods				
Initial pre-exposure window	84	272	0.31 (0.25-0.38)	Reference
1st exposed window	23	52	0.44 (0.28-0.66)	1.45 (0.91-2.31)
1st post-vaccination unexposed window	24	43	0.56 (0.36-0.83)	1.90 (1.21-2.99)
Subsequent exposed windows	10	31	0.32 (0.16-0.60)	1.07 (0.59-1.97)
Subsequent unexposed windows	14	24	0.57 (0.31-0.96)	2.02 (1.13-3.58)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 180 days

Table A8. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (narrow endpoint definition, 180-day risk window period, all patients n=207)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	175	454	0.39 (0.33-0.45)	Reference
180-day post-exposed window periods (all combined)	97	217	0.45 (0.36-0.55)	1.16 (0.91-1.48)
Individual window periods				
Initial pre-exposure window	166	431	0.39 (0.33-0.45)	Reference
1st exposed window	68	140	0.48 (0.38-0.61)	1.24 (0.95-1.63)
1st post-vaccination unexposed window	7	18	0.38 (0.15-0.79)	1.08 (0.50-2.34)
Subsequent exposed windows	29	77	0.38 (0.25-0.54)	1.02 (0.69-1.50)
Subsequent unexposed windows	<6	-	0.40 (0.05-1.45)	1.16 (0.28-4.79)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 180 days

Table A9. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (narrow endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=130)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	91	289	0.32 (0.25-0.39)	Reference
180-day post-exposed window periods (all combined)	64	134	0.48 (0.37-0.61)	1.55 (1.13-2.14)
Individual window periods				
Initial pre-exposure window	84	272	0.31 (0.25-0.38)	Reference
1st exposed window	45	87	0.52 (0.38-0.69)	1.70 (1.19-2.44)
1st post-vaccination unexposed window	<6	-	0.38 (0.12-0.88)	1.33 (0.52-3.43)
Subsequent exposed windows	19	47	0.41 (0.24-0.63)	1.38 (0.83-2.28)
Subsequent unexposed windows	<6	-	0.61 (0.07-2.20)	2.33 (0.56-9.75)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 90 days

Table A10. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (broad endpoint definition, 90-day risk window period, all patients n=346)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	347	898	0.39 (0.35-0.43)	Reference
90-day post-exposed window periods (all combined)	90	215	0.42 (0.34-0.52)	1.08 (0.86-1.36)
Individual window periods				
Initial pre-exposure window	263	728	0.36 (0.32-0.41)	Reference
1st exposed window	57	136	0.42 (0.32-0.54)	1.17 (0.88-1.55)
1st post-vaccination unexposed window	54	106	0.51 (0.38-0.67)	1.47 (1.11-1.97)
Subsequent exposed windows	33	79	0.42 (0.29-0.59)	1.19 (0.84-1.68)
Subsequent unexposed windows	30	64	0.47 (0.32-0.67)	1.38 (0.94-2.01)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 90 days

Table A11. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (broad endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus*** *n=244)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	226	637	0.35 (0.31-0.40)	Reference
90-day post-exposed window periods (all combined)	61	149	0.41 (0.31-0.53)	1.16 (0.88-1.53)
Individual window periods				
Initial pre-exposure window	157	515	0.30 (0.26-0.36)	Reference
1st exposed window	38	96	0.40 (0.28-0.54)	1.33 (0.93-1.89)
1st post-vaccination unexposed window	44	78	0.57 (0.41-0.76)	1.97 (1.40-2.75)
Subsequent exposed windows	23	53	0.43 (0.27-0.65)	1.52 (1.01-2.29)
Subsequent unexposed windows	25	45	0.56 (0.36-0.83)	2.02 (1.32-3.11)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 180 days

Table A12. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (broad endpoint definition, 180-day risk window period, all patients n=346)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	283	768	0.37 (0.33-0.41)	Reference
180-day post-exposed window periods (all combined)	154	344	0.45 (0.38-0.52)	1.23 (1.02-1.50)
Individual window periods				
Initial pre-exposure window	263	728	0.36 (0.32-0.41)	Reference
1st exposed window	101	227	0.44 (0.36-0.54)	1.24 (0.99-1.55)
1st post-vaccination unexposed window	16	32	0.50 (0.29-0.81)	1.52 (0.89-2.58)
Subsequent exposed windows	53	117	0.45 (0.34-0.59)	1.32 (0.99-1.77)
Subsequent unexposed windows	<6	-	0.48 (0.13-1.23)	1.46 (0.53-4.02)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 180 days

Table A13. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the IMRD UK database (broad endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=244)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	175	546	0.32 (0.27-0.37)	Reference
180-day post-exposed window periods (all combined)	112	240	0.47 (0.38-0.56)	**1.50 (1.19-1.90)**
Individual window periods				
Initial pre-exposure window	157	515	0.30 (0.26-0.36)	Reference
1st exposed window	72	159	0.45 (0.35-0.57)	**1.52 (1.15-2.01)**
1st post-vaccination unexposed window	14	25	0.57 (0.31-0.95)	**2.04 (1.13-3.70)**
Subsequent exposed windows	40	82	0.49 (0.35-0.67)	**1.75 (1.24-2.47)**
Subsequent unexposed windows	<6	-	0.65 (0.18-1.66)	2.44 (0.88-6.81)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 90 days

Table A14. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (narrow endpoint definition, 90-day risk window period, all patients n=198)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	220	471	0.47 (0.41-0.53)	Reference
90-day post-exposed window periods (all combined)	37	85	0.43 (0.30-0.60)	0.91 (0.65-1.26)
Individual window periods				
Initial pre-exposure window	188	406	0.46 (0.40-0.53)	Reference
1st exposed window	36	82	0.44 (0.31-0.60)	0.93 (0.66-1.30)
1st post-vaccination unexposed window	31	61	0.51 (0.34-0.72)	1.13 (0.77-1.67)
Subsequent exposed windows	<6	-	--	--
Subsequent unexposed windows	<6	-	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 90 days

Table A15. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (narrow endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=128)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	131	304	0.43 (0.36-0.51)	Reference
90-day post-exposed window periods (all combined)	26	56	0.47 (0.31-0.68)	1.06 (0.71-1.59)
Individual window periods				
Initial pre-exposure window	103	262	0.39 (0.32-0.48)	Reference
1st exposed window	26	54	0.48 (0.32-0.71)	1.24 (0.83-1.86)
1st post-vaccination unexposed window	27	39	0.68 (0.45-1.00)	1.86 (1.21-2.86)
Subsequent exposed windows	0	2	--	--
Subsequent unexposed windows	<6	-	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 180 days

Table A16. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (narrow endpoint definition, 180-day risk window, all patients n=198)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	195	426	0.46 (0.40-0.53)	Reference
180-day post-exposed window periods (all combined)	62	130	0.48 (0.36-0.61)	1.02 (0.77-1.36)
Individual window periods				
Initial pre-exposure window	188	406	0.46 (0.40-0.53)	Reference
1st exposed window	62	130	0.48 (0.37-0.61)	1.02 (0.77-1.35)
1st post-vaccination unexposed window	7	20	0.35 (0.14-0.72)	0.83 (0.35-1.98)
Subsequent exposed windows	0	0	--	--
Subsequent unexposed windows	--	--	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 180 days

Table A17. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (narrow endpoint definition, 180-day risk window,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=128)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	110	275	0.40 (0.33-0.48)	Reference
180-day post-exposed window periods (all combined)	47	84	0.56 (0.41-0.74)	**1.39 (1.01-1.92)**
Individual window periods				
Initial pre-exposure window	103	262	0.39 (0.32-0.48)	Reference
1st exposed window	47	84	0.56 (0.41-0.75)	**1.43 (1.03-1.98)**
1st post-vaccination unexposed window	7	13	0.54 (0.22-1.12)	1.56 (0.67-3.67)
Subsequent exposed windows	0	0	--	--
Subsequent unexposed windows	--	--	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 90 days

Table A18. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (broad endpoint definition, 90-day risk window, all patients, n=319)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	343	756	0.45 (0.41-0.50)	Reference
90-day post-exposed window periods (all combined)	64	139	0.46 (0.35-0.59)	0.98 (0.76-1.26)
Individual window periods				
Initial pre-exposure window	292	651	0.45 (0.40-0.50)	Reference
1st exposed window	63	137	0.46 (0.35-0.59)	1.01 (0.78-1.30)
1st post-vaccination unexposed window	50	102	0.49 (0.37-0.65)	1.13 (0.83-1.53)
Subsequent exposed windows	<6	-	--	--
Subsequent unexposed windows	<6	-	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 90 days

Table A19. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (broad endpoint definition, 90-day risk window,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=225)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	221	534	0.41 (0.36-0.47)	Reference
90-day post-exposed window periods (all combined)	46	99	0.47 (0.34-0.62)	1.10 (0.81- 1.49)
Individual window periods				
Initial pre-exposure window	174	458	0.38 (0.33-0.44)	Reference
1st exposed window	46	97	0.47 (0.35-0.63)	1.24 (0.91-1.69)
1st post-vaccination unexposed window	46	73	0.63 (0.46-0.84)	1.72 (1.23-2.40)
Subsequent exposed windows	0	2	--	--
Subsequent unexposed windows	<6	-	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 180 days

Table A20. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (broad endpoint definition, 180-day risk window, all patients, n=319)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	303	683	0.44 (0.40-0.50)	Reference
180-day post-exposed window periods (all combined)	104	212	0.49 (0.40-0.59)	1.08 (0.87-1.34)
Individual window periods				
Initial pre-exposure window	292	651	0.45 (0.40-0.50)	Reference
1st exposed window	104	212	0.49 (0.40-0.59)	1.07 (0.87-1.33)
1st post-vaccination unexposed window	11	32	0.34 (0.17-0.61)	0.82 (0.42-1.59)
Subsequent exposed windows	0	0	--	--
Subsequent unexposed windows	--	--	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: IMRD UK

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 180 days

Table A21. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus and exposure to Vaxzevria vaccine in the IMRD UK database (broad endpoint definition, 180-day risk window,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=225)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	185	482	0.38 (0.33-0.44)	Reference
180-day post-exposed window periods (all combined)	82	150	0.55 (0.43-0.68)	**1.41 (1.10-1.80)**
Individual window periods				
Initial pre-exposure window	174	458	0.38 (0.33-0.44)	Reference
1st exposed window	82	150	0.55 (0.44-0.68)	**1.43 (1.11-1.83)**
1st post-vaccination unexposed window	11	24	0.46 (0.23-0.82)	1.30 (0.67-2.53)
Subsequent exposed windows	0	0	--	**--**
Subsequent unexposed windows	--	--	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 90 days

Table A22. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period, all patients n=350)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	449	994	0.45 (0.41-0.50)	Reference
90-day post-exposed window periods (all combined)	67	163	0.41 (0.32-0.52)	0.89 (0.69-1.15)
Individual window periods				
Initial pre-exposure window	346	799	0.43 (0.39-0.48)	Reference
1st exposed window	41	106	0.39 (0.28-0.53)	0.89 (0.65-1.22)
1st post-vaccination unexposed window	60	126	0.48 (0.36-0.61)	1.10 (0.85-1.41)
Subsequent exposed windows	26	57	0.46 (0.30-0.67)	1.01 (0.70-1.46)
Subsequent unexposed windows	43	69	0.62 (0.45-0.84)	1.42 (1.04-1.95)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 90 days

Table A23. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=241)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	253	684	0.37 (0.33-0.42)	Reference
90-day post-exposed window periods (all combined)	45	113	0.40 (0.29-0.53)	1.05 (0.76-1.47)
Individual window periods				
Initial pre-exposure window	174	547	0.32 (0.27-0.37)	Reference
1st exposed window	32	73	0.44 (0.30-0.62)	1.38 (0.95-2.00)
1st post-vaccination unexposed window	42	86	0.49 (0.35-0.66)	1.55 (1.11-2.16)
Subsequent exposed windows	13	40	0.32 (0.17-0.55)	1.01 (0.58-1.75)
Subsequent unexposed windows	37	50	0.74 (0.52-1.03)	2.38 (1.66-3.40)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 180 days

Table A24. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period, all patients n=350)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	384	863	0.45 (0.40-0.49)	Reference
180-day post-exposed window periods (all combined)	132	293	0.45 (0.38-0.53)	0.98 (0.82-1.19)
Individual window periods				
Initial pre-exposure window	346	799	0.43 (0.39-0.48)	Reference
1st exposed window	84	199	0.42 (0.34-0.52)	0.95 (0.76-1.19)
1st post-vaccination unexposed window	23	48	0.48 (0.30-0.72)	1.12 (0.75-1.67)
Subsequent exposed windows	48	95	0.51 (0.37-0.67)	1.16 (0.88-1.54)
Subsequent unexposed windows	15	16	0.94 (0.52-1.54)	2.30 (1.35-3.92)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Narrow

Risk window period: 180 days

Table A25. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=241)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	203	593	0.34 (0.30-0.39)	Reference
180-day post-exposed window periods (all combined)	95	204	0.47 (0.38-0.57)	**1.34 (1.04-1.72)**
Individual window periods				
Initial pre-exposure window	174	547	0.32 (0.27-0.37)	Reference
1st exposed window	59	133	0.44 (0.34-0.57)	**1.37 (1.02-1.84)**
1st post-vaccination unexposed window	17	33	0.51 (0.30-0.82)	**1.70 (1.04-2.78)**
Subsequent exposed windows	36	70	0.51 (0.36-0.71)	**1.63 (1.15-2.31)**
Subsequent unexposed windows	12	12	0.99 (0.51-1.72)	**3.34 (1.81-6.17)**

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 90 days

Table A26. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period, all patients n=510)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	630	1,453	0.43 (0.40-0.47)	Reference
90-day post-exposed window periods (all combined)	96	225	0.43 (0.35-0.52)	0.95 (0.77-1.17)
Individual window periods				
Initial pre-exposure window	494	1,187	0.42 (0.38-0.45)	Reference
1st exposed window	67	153	0.44 (0.34-0.56)	1.04 (0.81-1.33)
1st post-vaccination unexposed window	85	181	0.47 (0.38-0.58)	1.12 (0.90-1.39)
Subsequent exposed windows	29	72	0.41 (0.27-0.58)	0.89 (0.63-1.27)
Subsequent unexposed windows	51	85	0.60 (0.45-0.79)	1.36 (1.02-1.80)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 90 days

Table A27. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=360)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	371	1,027	0.36 (0.33-0.40)	Reference
90-day post-exposed window periods (all combined)	64	156	0.41 (0.32-0.52)	1.10 (0.84-1.44)
Individual window periods				
Initial pre-exposure window	271	840	0.32 (0.29-0.36)	Reference
1st exposed window	50	108	0.46 (0.34-0.61)	1.43 (1.06-1.93)
1st post-vaccination unexposed window	59	128	0.46 (0.35-0.59)	1.45 (1.09-1.92)
Subsequent exposed windows	14	49	0.29 (0.16-0.48)	0.86 (0.51-1.45)
Subsequent unexposed windows	41	58	0.70 (0.50-0.95)	2.16 (1.55-3.00)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 180 days

Table A28. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period, all patients n=510)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	549	1,276	0.43 (0.40-0.47)	Reference
180-day post-exposed window periods (all combined)	177	402	0.44 (0.38-0.51)	0.98 (0.83-1.15)
Individual window periods				
Initial pre-exposure window	494	1,187	0.42 (0.38-0.45)	Reference
1st exposed window	121	284	0.43 (0.35-0.51)	1.00 (0.83-1.21)
1st post-vaccination unexposed window	38	70	0.55 (0.39-0.75)	1.35 (0.98-1.86)
Subsequent exposed windows	56	118	0.47 (0.36-0.62)	1.06 (0.82-1.37)
Subsequent unexposed windows	17	19	0.90 (0.52-1.43)	2.13 (1.30-3.50)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Comirnaty

Endpoint definition: Broad

Risk window period: 180 days

Table A29. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Comirnaty vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=360)*

Exposure: Comirnaty	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	313	904	0.35 (0.31-0.39)	Reference
180-day post-exposed window periods (all combined)	122	279	0.44 (0.36-0.52)	1.23 (0.99-1.53)
Individual window periods				
Initial pre-exposure window	271	840	0.32 (0.29-0.36)	Reference
1st exposed window	83	195	0.42 (0.34-0.53)	**1.30 (1.02-1.67)**
1st post-vaccination unexposed window	28	51	0.55 (0.37-0.80)	**1.83 (1.23-2.72)**
Subsequent exposed windows	39	84	0.47 (0.33-0.64)	**1.42 (1.02-1.98)**
Subsequent unexposed windows	14	14	1.03 (0.56-1.73)	**3.37 (1.93-5.88)**

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Narrow

Risk window period: 90 days

Table A30. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period, all patients n=59)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	62	168	0.37 (0.28-0.47)	Reference
90-day post-exposed window periods (all combined)	12	29	0.41 (0.21-0.72)	1.12 (0.61-2.06)
Individual window periods				
Initial pre-exposure window	47	138	0.34 (0.25-0.45)	Reference
1st exposed window	<10	-	0.32 (0.12-0.69)	0.93 (0.40-2.20)
1st post-vaccination unexposed window	10	19	0.53 (0.26-0.98)	1.57 (0.81-3.05)
Subsequent exposed windows	<10	-	0.58 (0.21-1.26)	1.84 (0.79-4.32)
Subsequent unexposed windows	<10	-	0.46 (0.15-1.07)	1.51 (0.58-3.96)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Narrow

Risk window period: 90 days

Table A31. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=49)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	48	140	0.34 (0.25-0.46)	Reference
90-day post-exposed window periods (all combined)	10	24	0.42 (0.20-0.77)	1.23 (0.64-2.38)
Individual window periods				
Initial pre-exposure window	35	115	0.30 (0.21-0.42)	Reference
1st exposed window	<10	-	0.32 (0.10-0.75)	1.07 (0.42-2.70)
1st post-vaccination unexposed window	10	16	0.64 (0.31-1.18)	2.20 (1.14-4.24)
Subsequent exposed windows	<10	-	0.60 (0.20-1.41)	2.12 (0.82-5.50)
Subsequent unexposed windows	<10	-	0.34 (0.07-0.98)	1.22 (0.35-4.19)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Narrow

Risk window period: 180 days

Table A32. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period, all patients n=59)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	51	146	0.35 (0.26-0.46)	Reference
180-day post-exposed window periods (all combined)	23	51	0.45 (0.29-0.68)	1.32 (0.82-2.14)
Individual window periods				
Initial pre-exposure window	47	138	0.34 (0.25-0.45)	Reference
1st exposed window	14	37	0.37 (0.20-0.63)	1.09 (0.59-1.99)
1st post-vaccination unexposed window	<10	-	0.65 (0.18-1.65)	1.92 (0.70-5.26)
Subsequent exposed windows	<10	-	0.65 (0.30-1.24)	2.29 (1.11-4.74)
Subsequent unexposed windows	0	2	--	--

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Narrow

Risk window period: 180 days

Table A33. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=49)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	39	122	0.32 (0.23-0.44)	Reference
180-day post-exposed window periods (all combined)	19	42	0.45 (0.27-0.71)	1.46 (0.86-2.49)
Individual window periods				
Initial pre-exposure window	35	115	0.30 (0.21-0.42)	Reference
1st exposed window	13	31	0.42 (0.23-0.73)	1.37 (0.73-2.58)
1st post-vaccination unexposed window	<10	-	0.76 (0.21-1.96)	2.65 (0.96-7.29)
Subsequent exposed windows	<10	-	0.54 (0.20-1.17)	2.17 (0.86-5.46)
Subsequent unexposed windows	0	1	--	**--**

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Broad

Risk window period: 90 days

Table A34. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period, all patients n=92)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	91	262	0.35 (0.28-0.43)	Reference
90-day post-exposed window periods (all combined)	23	41	0.56 (0.35-0.83)	1.59 (1.03-2.46)
Individual window periods				
Initial pre-exposure window	70	218	0.32 (0.25-0.41)	Reference
1st exposed window	13	29	0.45 (0.24-0.76)	1.38 (0.76-2.50)
1st post-vaccination unexposed window	16	33	0.49 (0.28-0.80)	1.53 (0.89-2.63)
Subsequent exposed windows	10	12	0.82 (0.39-1.50)	2.70 (1.42-5.15)
Subsequent unexposed windows	<10	-	0.42 (0.14-0.97)	1.46 (0.56-3.82)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Broad

Risk window period: 90 days

Table A35. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=82)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	77	234	0.33 (0.26-0.41)	Reference
90-day post-exposed window periods (all combined)	21	36	0.58 (0.36-0.89)	**1.76 (1.13-2.76)**
Individual window periods				
Initial pre-exposure window	58	195	0.30 (0.23-0.39)	Reference
1st exposed window	12	26	0.46 (0.24-0.81)	1.55 (0.84-2.88)
1st post-vaccination unexposed window	16	29	0.55 (0.31-0.89)	**1.87 (1.08-3.22)**
Subsequent exposed windows	<10	-	0.89 (0.41-1.68)	**3.14 (1.58-6.24)**
Subsequent unexposed windows	<10	-	0.30 (0.06-0.87)	1.13 (0.33-3.84)

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Broad

Risk window period: 180 days

Table A36. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period, all patients n=92)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	78	232	0.34 (0.27-0.42)	Reference
180-day post-exposed window periods (all combined)	36	71	0.50 (0.35-0.70)	1.51 (1.03-2.20)
Individual window periods				
Initial pre-exposure window	70	218	0.32 (0.25-0.41)	Reference
1st exposed window	24	57	0.42 (0.27-0.63)	1.31 (0.81-2.10)
1st post-vaccination unexposed window	<10	-	0.62 (0.27-1.23)	2.00 (0.95-4.22)
Subsequent exposed windows	12	15	0.80 (0.42-1.41)	2.86 (1.55-5.28)
Subsequent unexposed windows	0	2	--	--

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Spikevax

Endpoint definition: Broad

Risk window period: 180 days

Table A37. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Spikevax vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus****, n=82)*

Exposure: Spikevax	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	66	208	0.32 (0.25-0.40)	Reference
180-day post-exposed window periods (all combined)	32	62	0.52 (0.35-0.73)	**1.64 (1.10-2.45)**
Individual window periods				
Initial pre-exposure window	58	195	0.30 (0.23-0.39)	Reference
1st exposed window	23	50	0.46 (0.29-0.69)	1.53 (0.94-2.50)
1st post-vaccination unexposed window	<10	-	0.67 (0.29-1.33)	**2.37 (1.12-5.04)**
Subsequent exposed windows	<10	-	0.73 (0.34-1.39)	**2.90 (1.41-5.95)**
Subsequent unexposed windows	0	1	--	**--**

95% CI: 95% Confidence intervals

N.B: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 90 days

Table A38. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period, all patients n=45)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	56	113	0.49 (0.37-0.64)	Reference
90-day post-exposed window periods (all combined)	11	20	0.54 (0.27-0.96)	1.08 (0.58-2.00)
Individual window periods				
Initial pre-exposure window	49	103	0.48 (0.35-0.63)	Reference
1st exposed window	11	20	0.56 (0.28-1.01)	1.20 (0.65-2.22)
1st post-vaccination unexposed window	<10	-	0.64 (0.24-1.40)	1.50 (0.67-3.36)
Subsequent exposed windows	0	1	--	--
Subsequent unexposed windows	<10	-	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 90 days

Table A39. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (narrow endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=29)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	29	73	0.40 (0.27-0.57)	Reference
90-day post-exposed window periods (all combined)	<10	-	0.38 (0.12-0.89)	0.94 (0.36-2.45)
Individual window periods				
Initial pre-exposure window	24	66	0.36 (0.23-0.54)	Reference
1st exposed window	<10	-	0.40 (0.13-0.93)	1.12 (0.42-2.99)
1st post-vaccination unexposed window	<10	-	0.64 (0.17-1.63)	2.01 (0.78-5.13)
Subsequent exposed windows	0	1	--	--
Subsequent unexposed windows	<10	-	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 180 days

Table A40. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period, all patients n=45)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	52	105	0.50 (0.37-0.65)	Reference
180-day post-exposed window periods (all combined)	15	29	0.52 (0.29-0.86)	1.04 (0.62-1.75)
Individual window periods				
Initial pre-exposure window	49	103	0.48 (0.35-0.63)	Reference
1st exposed window	15	29	0.52 (0.29-0.86)	1.09 (0.65-1.83)
1st post-vaccination unexposed window	<10	-	1.54 (0.32-4.50)	5.11 (1.33-19.53)
Subsequent exposed windows	--	--	--	--
Subsequent unexposed windows	--	--	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Narrow

Risk window period: 180 days

Table A41. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (narrow endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=29)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	27	68	0.40 (0.26-0.58)	Reference
180-day post-exposed window periods (all combined)	<10	-	0.38 (0.15-0.78)	0.94 (0.42-2.07)
Individual window periods				
Initial pre-exposure window	24	66	0.36 (0.23-0.54)	Reference
1st exposed window	<10	-	0.38 (0.15-0.78)	1.04 (0.47-2.29)
1st post-vaccination unexposed window	<10	-	1.92 (0.40-5.62)	10.89 (3.06-38.75)
Subsequent exposed windows	--	--	--	--
Subsequent unexposed windows	--	--	--	--

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 90 days

Table A42. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period, all patients n=86)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	98	219	0.45 (0.36-0.54)	Reference
90-day post-exposed window periods (all combined)	17	39	0.43 (0.25-0.70)	0.96 (0.59-1.57)
Individual window periods				
Initial pre-exposure window	84	196	0.43 (0.34-0.53)	Reference
1st exposed window	16	36	0.45 (0.26-0.73)	1.05 (0.63-1.74)
1st post-vaccination unexposed window	12	18	0.68 (0.35-1.19)	1.80 (0.99-3.25)
Subsequent exposed windows	<10	-	--	--
Subsequent unexposed windows	<10	-	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 90 days

Table A43. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (broad endpoint definition, 90-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=59)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	60	151	0.40 (0.30-0.51)	Reference
90-day post-exposed window periods (all combined)	<10	-	0.30 (0.13-0.59)	0.74 (0.36-1.54)
Individual window periods				
Initial pre-exposure window	49	134	0.37 (0.27-0.48)	Reference
1st exposed window	<10	-	0.29 (0.12-0.61)	0.81 (0.37-1.81)
1st post-vaccination unexposed window	<10	-	0.71 (0.32-1.34)	2.30 (1.15-4.60)
Subsequent exposed windows	<10	-	--	--
Subsequent unexposed windows	<10	-	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 180 days

Table A44. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period, all patients n=86)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	89	202	0.44 (0.35-0.54)	Reference
180-day post-exposed window periods (all combined)	26	56	0.47 (0.30-0.68)	1.05 (0.71-1.56)
Individual window periods				
Initial pre-exposure window	84	196	0.43 (0.34-0.53)	Reference
1st exposed window	26	56	0.47 (0.30-0.68)	1.09 (0.73-1.63)
1st post-vaccination unexposed window	<10	-	0.77 (0.25-1.79)	2.80 (0.98-7.97)
Subsequent exposed windows	--	--	--	--
Subsequent unexposed windows	--	--	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.

Database: THIN® Spain

Vaccine: Vaxzevria

Endpoint definition: Broad

Risk window period: 180 days

Table A45. *Self-controlled case series (SCCS) analysis: Association between pemphigoid or pemphigus* and *exposure to Vaxzevria vaccine in the THIN® Spain database (broad endpoint definition, 180-day risk window period,* ***excluding patients with prior history of pemphigoid or pemphigus,*** *n=59)*

Exposure: Vaxzevria	Events	Follow-up time (person years)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Unexposed window periods (all combined)	54	139	0.39 (0.29-0.51)	Reference
180-day post-exposed window periods (all combined)	14	38	0.36 (0.20-0.61)	0.93 (0.54-1.61)
Individual window periods				
Initial pre-exposure window	49	134	0.37 (0.27-0.48)	Reference
1st exposed window	14	38	0.36 (0.20-0.61)	1.00 (0.57-1.74)
1st post-vaccination unexposed window	<10	-	0.89 (0.29-2.07)	3.78 (1.25-11.38)
Subsequent exposed windows	--	--	--	--
Subsequent unexposed windows	--	--	--	**--**

95% CI: 95% Confidence intervals

N.B.$_1$: Subsequent exposed and unexposed windows were not assessed because only two doses of Vaxzevria were administered to patients, therefore, there was only one treatment window, i.e., the first and second exposed windows coalesced to form a single window (1st exposed window).

N.B.$_2$: Repeated events were allowed within a 180 day-period, i.e., events coded within 180 days of a previous coded event (or a string of events within 180 days of each other) were assumed to be a single event starting on the earliest date.