29 November 2022

FINAL Data analysis report

Title: Incidence rates of vulval ulceration following Comirnaty vaccine

Administrative details of the data analysis	
Substance(s)	Tozinameran / Comirnaty (COVID-19 mRNA vaccine)
Condition/ADR(s)	Vulval ulceration
Short title of topic	Vulval ulceration and Comirnaty
TDA-DAT lead analyst (and reviewer)	Robert Flynn (Denise Umuhire, Maria Clara Restrepo-Mendez)

1. List of abbreviations

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

2. Rationale and background

Vulval ulcerations are painful and distressing ulcers of the vulva or lower vagina. They can be caused by sexually transmitted infections (most commonly herpes simplex virus – HSV) or non-sexually transmitted infections, autoimmune conditions, drug reactions, and local manifestations of systemic illness [1]

Non-sexually acquired acute genital ulceration, also known as *Lipschütz ulcer* and *ulcus vulvae acutum* is a rare condition involving painful vulvar ulcers without an identifiable aetiology [1,2]. It is an uncommon, self-limiting, non-sexually transmitted condition characterised by a sudden onset of painful, necrotic ulcerations of the vulva or lower vagina which typically occurs in sexually inactive adolescent girls or young women and may be preceded by flu-like symptoms. The condition has been associated with acute viral and bacterial infections, particularly Epstein-Barr virus (EBV) infection.

During routine signal detection activities, cases of genital ulceration (including vulval ulceration, vaginal ulceration, vulvovaginal ulceration, genital ulceration) in close temporal association to Comirnaty vaccination were identified and reported from national reports, EudraVigilance and literature. Noting particularly these events in younger females who were not sexually active and those indicating positive rechallenge, the potential causal relationship between the events and vaccination with Comirnaty is being further investigated. To support the assessment of the signal, estimates are generated on the use of the vaccines in the general population, and incidence rates for vulval ulcerations in the general and exposed female population.

3. Research question and objectives

The objectives of the study were to describe:

1. Comirnaty vaccine exposure stratified by age, number of doses, and year of vaccination.
2. Incidence rates of vulval ulceration in the general population stratified by age and year.
3. Incidence rates of vulval ulceration following exposure to Comirnaty vaccine stratified by age, number of doses and year.
4. Incidence rates of vulval ulceration following exposure to other COVID-19 vaccines stratified by age, number of doses and year.

4. Research methods

4.1. Study design

This was a cohort study describing vaccine exposure, population incidence rates of vulval ulceration and incidence rates of vulval ulceration in the vaccine exposed population.

4.2. Setting and study population

The study population was the general female population in the UK and female patients visiting general practices in Spain.

4.3. Data sources

The following in-house databases were used: IQVIA™ Medical Research Data (IMRD) UK and The Health Improvement Network (THIN®) Spain. Brief descriptions of these databases are provided in Annex 1. Other in-house data sources do not capture COVID-19 vaccines sufficiently completely or accurately.

4.4. Variables

Exposure

In IMRD UK database, COVID-19 vaccine exposures are identified as prescribed medicines with data captured by point of care systems accredited to support the delivery of COVID-19 vaccinations: this is automatically fed back into the GP clinical system. A good level of completeness for recording of COVID-19 vaccination status and dates of dose are expected, although it is not known if this has been validated for research purposes.

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

Annex 2 shows the codes that were used for each database.

Outcome

Vulval ulceration was identified through Read codes for IMRD UK database and ICD10 codes for the THIN® Spain database (See Annex 2). The main analysis was based on codes considered to be more specific for idiopathic vulval ulceration, excluding codes where there was a known aetiology (see list in Annex 2).

Other variables

Vaccine utilisation was stratified by age group and number of doses. Event rates for vulval ulceration in the general population were stratified by age group and year. Event rates among exposed patients were stratified by age, and number of doses. Age was categorised as: < 10; 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80 years.

4.5. Statistical analysis

4.5.1. Main statistical methods

1.Vaccine exposure: We described vaccine exposure as counts of patients who received Comirnaty vaccine stratified by age, number of doses, and year.

2. Event rates in the general population: We describe the incidence of new onset vulval ulceration in female patients contributing patient time to the databases listed above (mostly likely in the years pre-dating the COVID-19 vaccination campaigns). Patients were required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients were excluded from the analysis if they had any prior history of any of the selected codes for vulval ulceration in the database. The study period varied according to the years of coverage in the two databases (UK, and Spain). For IMRD UK database, the covered period was from 2012 to 2019. For THIN® Spain, the covered period was from 2014 to 2019.

- Numerator: The numerator consisted of the number of patients who experience the event of interest (vulval ulceration) during the yearly time period. Patients with a baseline history of vulval ulceration were excluded. Included patients were only permitted to contribute one event each.

- Denominator: The denominator was defined as patient follow-up time. As with the numerators, patients with a baseline history of vulval ulceration at the start of each period were excluded. Patient follow-up time was truncated at the occurrence of the first event after which they did not contribute to the analysis.

Follow-up time was calculated using the following formula:

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

Time was truncated where patients left the study cohort part way through a time period or where they had an event.

The incidence rate for vulval ulceration was defined as the number of events divided by the total follow up time. The incidence rate was calculated using the following formula:

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

The incidence rates are presented as the number of events per 100,000 person-years and were calculated for the entire population as well as stratified by age group < 10; 10-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80 years). Confidence intervals around incidence rates was calculated using exact method.

3. Event rates among exposed patients: To describe the event rate of new onset vulval ulceration following exposure to the vaccine, a rate was calculated using a similar methodology described in section (2) above but restricted to only those patients known to have been exposed to the vaccine. Exposed patients were followed up for a maximum of 30-day following first exposure, a cut-off subject to sensitivity analyses. Thus, the incidence rate was calculated as new onset events divided by the total duration of follow-up time in years. Patients were censored from the analysis if they left the population (i.e., moved practice, died, or reached the end of follow-up for their practice), or when they were exposed to an alternative COVID-19 vaccine.

Event rates were stratified by the age groups described above. The primary analysis considered the 30-day period after the initial vaccine. A secondary analysis looked at the second and subsequent exposures to the vaccine. The period covered was from December 2020 to June 2022 for both the UK and Spain.

4. Event rates among exposed patients to other COVID-19 vaccines: The same analysis described in (3) was run with an alternative COVID-19 vaccine used as a comparator. For IMRD UK database, the comparator was Vaxzevria as this was the second most widely use vaccine in the UK. For THIN® Spain database, the comparators were Spikevax (more widely used in Spain, but an RNA vaccine similar to Comirnaty) and Vaxzevria (less widely used in Spain but using a different technology to Comirnaty). To compare event rates between Comirnaty and the comparator vaccine, event rates were standardised by age (females only) to a standard European reference population [3]. This is because COVID-19 vaccines were typically used in different age groups and although vaginal ulceration is recorded across all ages, it seems to be less common in the very young and very old. The period covered was from January 2020 to June 2022 for both the UK and Spain.

In accordance with database rules on the management of low cell counts, cells with low numbers (<6 in the IMRD database and <10 in the THIN® database) will be removed prior to publication. Additional cells may be redacted (events/patients typically being rounded up to the nearest 10) if needed to ensure that the aforementioned low cell counts cannot be reidentified. This may include both events/patients and follow-up times.

4.5.2. Exploratory analysis: Self-controlled Case Series

As this signal involves a transient exposure for which risk windows can reliably be constructed, and because the outcome is a rare but acute event, the use of a Self-controlled Case Series (SCCS) design was explored [4,5]. The key elements of this are described below:

Data source: IMRD UK

Study cohort: Patients vaccinated with Comirnaty AND with diagnoses of vulval/vaginal ulceration from 2019 onwards. Follow-up started 1-year after first entry onto database.

Event definition: As defined in section 4.4 above. In this analysis, repeated events were allowed. Events coded within 30 days of a previous coded event (or a string of events within 30 days of each other) were assumed to be a single event starting on the earliest date.

Risk window: 30 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+30 days (or censored)
Post-vaccination "unexposed":	**from** 1st vaccination date+30 days **to** 2nd vaccination (or censored)
Subsequent vaccination "exposed":	**from** n^{th} vaccination date

to n^{th} vaccination date + 30 days (or censored). Consecutive vaccinations within the risk window to be coalesced into a single window.

Subsequent post-vaccination "unexposed": **from** n^{th} subsequent vaccination date + 30 days
to n^{th} subsequent vaccination (or censored)

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

The following assumptions were implicit in the analysis:

- No confounding by age since we assessed a short duration of follow-up and vulva ulceration occurs across all ages.
- Occurrence of the event is not expected to influence subsequent likelihood of vaccination.
- Occurrence of the event does not prohibit subsequent vaccination.
- Occurrence of the event is not associated with increased risk of death.
- Event rates are constant within time windows: the outcome event codes are used reasonably consistently between 2019 and 2022.

Methods: We compared event rates (n events / follow-up time) in not-at-risk "unexposed" windows with at risk "exposed" time windows. Model events (using a conditional Poisson model) rate to give a relative incidence rate. Compare initial "at-risk" window with subsequent "at-risk" windows.

The period covered was from 01 Jan 2019 to 01 June 2022.

4.5.3. Sensitivity analysis

For the **main analysis**, sensitivity analyses included calculating event rates in exposed subjects over 90 days follow-up post vaccination (as opposed to 30 days). In addition, a broader endpoint definition was used to include vulval/vaginal ulceration of known cause. As well as following up from the initial vaccine exposure, we also calculated event rates following second and third vaccinations.

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

- A 60/90-day risk window (instead of 30 days)
- A broader range of Read codes (to include vulval/vaginal ulceration where there is an established cause)
- Exclusion of patients with history of event at start of follow-up
- Expanding the 30-day cut-off for discrete events to 60 days
- Exclude patients who did not survive to end of follow-up (01 June 2022)

Analyses were done using SAS for IMRD UK and THIN® Spain databases.

4.6. 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 a 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

5.1. Vaccine exposure

Table 1 shows the number of female patients with a prescription for Comirnaty and other COVID-19 vaccines and the number of vaccinations in both the IMRD UK and THIN® Spain databases. Numbers are also presented stratified by age group and year.

In the **IMRD EMIS UK** database, 45% of vaccinated female patients with Comirnaty were between 20 to 49 years of age and 47% of those vaccinated with Vaxzevria were between 40 to 59 years of age.

There was heterogeneity in the vaccine regiments used:

- 45% of vaccinated females initially received two consecutive doses of Comirnaty. Of these, 56% subsequently had a third dose of Comirnaty and 32% had received no further vaccine by the end of follow-up. The remainder of patients received a vaccine other than Comirnaty for their third dose.
- 42% of vaccinated females initially received two consecutive doses of Vaxzevria. Of these, 62% subsequently had Comirnaty as the third vaccine, 16% had received no further vaccine by the end of follow-up. The remainder of patients received a vaccine other than Comirnaty for their third dose.

Across all vaccine regimens in the UK, the median elapsed time between first dose and second dose was 76 days.

In the **THIN® Spain** database, 48% of vaccinated female patients with Comirnaty were between 30 to 59 years of age, 64% of those vaccinated with Spikevax were between 40 to 69 years of age, and 58% of those vaccinated with Vaxzevria were between 60 to 69 years of age.

Again, there was heterogeneity in the vaccine regiments used:

- 60% of vaccinated females initially received two consecutive doses of Comirnaty. Of these, 48% had received no further vaccine by the end of follow-up, 28% subsequently had a third dose of Spikevax and 24% subsequently had a third dose of Comirnaty.

- 13% of female patients initially received two consecutive doses of Spikevax. Of these, 39% subsequently had a third dose of Spikevax, 60% 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.
- 13% of vaccinated female patients initially received two consecutive doses of Vaxzevria. Of these, 78% subsequently had a third dose of Spikevax, 16% 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.

Across all vaccine regimens in Spain, the median elapsed time between first dose and second dose was 21 days.

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

	IMRD UK				THIN® Spain					
	Comirnaty		Vaxzevria		Comirnaty		Spikevax		Vaxzevria	
	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations	N patients	N vaccinations
Overall	551,450	1,044,898	283,560	551,327	330,058	689,843	219,671	306,602	67,877	130,573
Age at first use (years)										
<10	3,707	3,813	<6	<6	10,279	17,307	<10	<10	<10	<10
10-19	58,008	104,693	<2,400	<4,260	44,605	83,712	<5,350	<7,560	571	1,043
20-29	90,413	181,242	17,818	33,578	36,220	67,826	26,269	41,323	4,301	7,964
30-39	95,364	194,192	30,667	58,793	47,806	92,072	35,828	56,599	5,507	10,159
40-49	64,737	110,649	62,133	120,725	61,966	122,926	46,712	59,189	7,173	13,286
50-59	71,908	120,556	70,683	138,559	50,074	101,435	51,204	70,295	10,839	20,601
60-69	63,731	108,556	50,366	99,082	14,362	27,312	43,850	47,612	39,456	77,488
70-79	61,650	120,022	35,754	70,293	38,119	102,680	6,370	14,229	26	27
≥80	41,932	101,175	13,899	26,043	26,627	74,573	4,087	9,798	<10	<10
Year										
2020	14,701	15,090	98	168	1,979	4,858	N/A	N/A	N/A	N/A
2021	491,593	902,596	283,246	550,616	311,076	658,933	135,816	222,232	67,858	130,554
2022	45,156	127,212	216	543	17,003	26,052	83,855	84,370	19	19

5.2. Event rates in the general population

Table 2 shows the overall population event rate for vulval ulceration and stratified by age group for the **IMRD UK** and **THIN® Spain** databases. In both databases, there was no clear pattern of increase in the incidence of vulval ulceration with age. However, female subjects aged 70 or older had a higher incidence of vulval ulceration in comparison with other age groups in the **IMRD UK** database.

There was no difference in the incidence rates of vulval ulceration when using the codes considered to be more specific for idiopathic vulval ulceration and when including the codes stating a known aetiology (**broader endpoint definition**) in the **IMRD UK** database (**Table 2**).

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

Strata	IMRD 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	137	6,383,805	2.15 (1.80-2.54)	126	2,419,154	5.21 (4.34-6.20)
Age at first use (years)						
<10	<6	-	0.13 (0.00-0.73)	<10	-	1.42 (0.29-4.14)
10-19	<20	-	1.58 (0.76-2.91)	<20	-	6.68 (3.74-11.01)
20-29	15	783,39	1.91 (1.07-3.16)	20	246,155	8.12 (4.96-12.55)
30-39	15	922,000	1.63 (0.91-2.68)	17	360,131	4.72 (2.75-7.56)
40-49	23	919,826	2.50 (1.59-3.75)	14	388,047	3.61 (1.97-6.05)
50-59	15	834,886	1.80 (1.01-2.96)	12	339,139	3.54 (1.83-6.18)
60-69	18	664,579	2.71 (1.61-4.28)	16	276,543	5.79 (3.31-9.40)
70-79	22	492,183	4.47 (2.80-6.77)	16	205,827	7.77 (4.44-12.62)
≥80	18	368,139	4.89 (2.90-7.73)	13	166,676	7.80 (4.15-13.34)
Broad event definition						
Overall	149	6,383,076	2.33 (1.97-2.74)	N/A	N/A	N/A
Age at first use (years)						
<10	<6	-	0.26 (0.03-0.94)	N/A	N/A	N/A
10-19	<20	-	1.74 (0.87-3.12)	N/A	N/A	N/A
20-29	16	783,332	2.04 (1.17-3.32)	N/A	N/A	N/A
30-39	16	921,852	1.74 (0.99-2.82)	N/A	N/A	N/A
40-49	23	919,627	2.50 (1.59-3.75)	N/A	N/A	N/A
50-59	20	834,748	2.40 (1.46-3.70)	N/A	N/A	N/A
60-69	21	664,472	3.16 (1.96-4.83)	N/A	N/A	N/A
70-79	22	492,132	4.47 (2.80-6.77)	N/A	N/A	N/A
≥80	18	368,124	4.89 (2.90-7.73)	N/A	N/A	N/A

N/A = not applicable; follow-up time was redacted for event counts if indicated as <6, <10 or <20

5.3. Standardised event rates in the general population

There was no difference between the overall population event rate (non-standardised) in comparison to the standardised event rate for vulval ulceration in either the **IMRD UK** or **THIN® Spain** database (**Table 3**).

It is worth noticing that the incidence rate for vulval ulceration was higher in the **THIN® Spain database** than the IMRD UK database.

Standardised rates were estimated to allow comparisons of vaccines (see section 6.4) which had been given to cohorts with different age structures.

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

Strata	Events	Follow-up time (person years)	Overall population event rates	
			Non-standardised	Standardised
			Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)
IMRD UK	137	6,383,805	2.15 (1.80-2.54)	2.31 (1.94-2.73)
IMRD UK broad event definition	149	6,383,076	2.33 (1.97-2.74)	2.51 (2.12-2.94)
THIN® Spain	126	2,419,154	5.21 (4.34-6.20)	5.31 (4.42-6.30)

5.4. Event rates among subjects exposed to Comirnaty and other COVID-19 vaccines

Table 4 shows standardised **vaccine-exposed** incidence rates of vulval ulceration following first, second, and third dose in both the **IMRD UK** and **THIN® Spain** databases stratified by type of vaccine and vaccine window (either 30 or 90 days after receiving vaccination).

In the **IMRD UK database**, in the analysis looking at incidence rates of vulval ulceration after 30 days following first dose of Comirnaty (**Table 4**, first row), there was a single event, however, the 95% confidence interval for the observed event rates overlapped with the expected event range in the population (**Table 3**). Three female patients had a diagnosis of vulval ulceration up to 90 days of follow-up, however, the 95% confidence interval for the observed event rates were within the expected event range in the population. Similar results were observed after 30 and 90 days following the second dose of Comirnaty. After 90 days following the third dose of Comirnaty, 3 female patients had a diagnosis of vulval ulceration, however, the 95% confidence interval for the observed event rates were within the expected event range in the population.

Similar results were observed when looking at other COVID-19 vaccines and when looking at the **THIN® Spain** databases (**Table 4**).

In general, the upper confidence intervals of the incidence rates were relatively high due to a limited number of follow-up years in each stratum.

Table 4. Standardised incidence rates of new onset vulval ulceration per 100,000 years of follow-up following exposure to COVID-19 vaccines

Database / event definition	Vaccine	Vaccine window	After receiving first dose	After receiving second dose	After receiving third dose
			Rate* per 100,000 (95% CI)	Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)
IMRD UK	**Comirnaty**	**30-day**	4.34 (0.11-20.29)	3.66 (0.09-17.12)	0.00 (.-.)
	Vaxzevria	30-day	14.88 (1.44-48.63)	5.67 (0.68-18.22)	0.00 (.-.)
	Comirnaty	**90-day**	4.64 (0.84-12.62)	3.53 (0.69-9.52)	7.19 (1.19-19.79)
	Vaxzevria	90-day	6.84 (1.22-17.48)	4.18 (1.12-9.98)	0.00 (.-.)
IMRD UK / broad event definition	**Comirnaty**	**30-day**	4.34 (0.11-20.29)	3.66 (0.09-17.12)	0.00 (.-.)
	Vaxzevria	30-day	14.88 (1.44-48.63)	5.67 (0.68-18.22)	0.00 (.-.)
	Comirnaty	**90-day**	4.64 (0.84-12.62)	3.53 (0.69-9.52)	7.19 (1.19-19.79)
	Vaxzevria	90-day	6.84 (1.23-17.48)	4.19 (1.12-9.98)	0.00 (.-.)
THIN® Spain	**Comirnaty**	**30-day**	7.20 (0.84-23.18)	4.28 (0.11-19.99)	4.24 (0.11-19.80)
	Spikevax	30-day	9.98 (0.25-46.63)	0.00 (.-.)	0.00 (.-.)
	Vaxzevria	30-day	0.00 (.-.)	0.00 (.-.)	0.00 (.-.)
	Comirnaty	**90-day**	4.90 (1.33-11.67)	8.86 (3.16-18.40)	2.76 (0.33-8.87)
	Spikevax	90-day	3.53 (0.09-16.52)	0.00 (.-.)	0.00 (.-.)
	Vaxzevria	90-day	1.42 (0.04-6.65)	0.00 (.-.)	0.00 (.-.)

*For any time-window, there were less than 10 events identified in each database and regardless of the event definition. There is some (limited) double counting of events as a single event may occur within 30 (or 90) days of both the first and second vaccines.

5.5. Exploratory analysis: Self-controlled Case Series

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. (4,5) Incidence rate ratios are derived comparing the rate of events during **exposed periods of time** with the rate during **all other observed time periods**. A major advantage of this design is that the potential confounding effect of both recorded and unrecorded characteristics that vary between individuals, but are fixed over time within individuals, is removed (4,5) (i.e., comparisons are made within individuals, therefore, individuals act as their own control).

For this study, we identified all female subjects with at least one incident vulval ulceration during the follow-up time (from 01Jan2019 to 01Jun2022) and exposed to Comirnaty. Periods of follow-up with no exposure to Comirnaty were classified as "unexposed window". Follow-up 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 30-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 vulval ulceration remains constant during the time period and was not affected by exposure to Comirnaty vaccine.

Forty-three patients were included in the SCCS, followed up for a total of **141 person-years** and in whom **47 events** were recoded. **There was no increase in the incidence rate of vulval ulceration in the period after vaccination** (**Table 5**), although confidence intervals are wide. Similar results were obtained when looking individually at subsequent exposed and unexposed windows - i.e., after receiving the first, second and third dose (data available upon request).

Further sensitivity analyses: (i) extended the 30-days post-vaccination "exposure" window to 60- and 90-day post exposure windows, ii) used the broader endpoint definition, iii) excluded patients who had a history of the outcome at baseline, iv) used a 60-day rather than a 30-day cut-off for describing discrete events (which meant that events recorded as occurring within 60 days of each other counted as a single event), and v) excluded patients who did not survive until the end of follow-up. **These additional analyses had very little impact on the results.** Although it should be noted that extending the cut-off for discrete events had the effect of removing one of "exposed" events, so the exposed rate dropped below that of the unexposed rate. All data are available upon request.

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

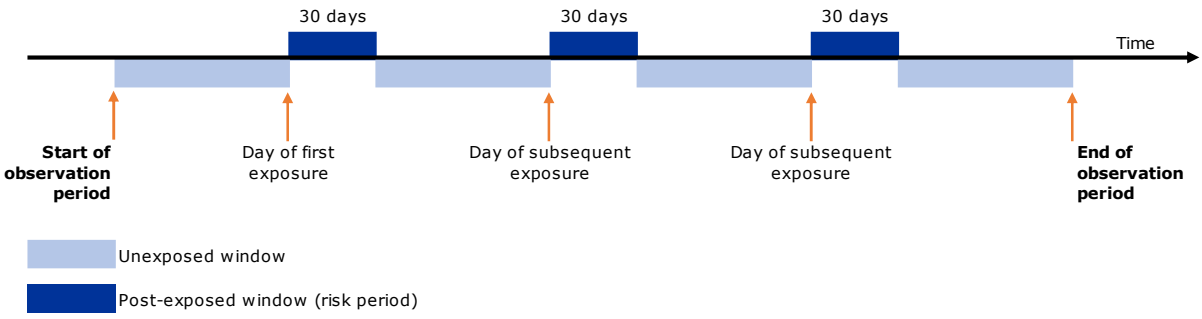

*Table 5. Self-controlled case series (SCCS) analysis: Association between exposure to Comirnaty vaccine and vulval ulceration in the **IMRD UK database***

Exposure	Events	Follow-up time (person years)	Incidence rate (95% CI)	Relative risk (95% CI)
Unexposed window periods	43	131	0.33 (0.24-0.44)	--
30-day post-exposed window periods	<6	-	0.39 (0.11-1.00)	--
Post-exposed window / Unexposed window	--	--	--	**1.16 (0.43-3.09)**

6. Discussion

6.1. Key results

- While Comirnaty and Vaxzevria were the most common vaccines prescribed in IMRD EMIS UK database, Comirnaty and Spikevax were the most common in THIN Spain database.
- There was heterogeneity in the vaccine regiments used in both databases, including use of homologous and heterologous booster vaccinations.
- The use of Comirnaty and other COVID-19 vaccines also differed by age group. Around 60% of female patients who received Comirnaty were aged <50 years in both databases. In contrast, around 60% and 70% of female patients who received Vaxzevria were aged 50 years or older in the IMRD UK and THIN® Spain databases, respectively.
- The incidence rate of vulval ulceration was more than 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. Alternatively, there might be a true different in the burden of the disease between the two populations.
- There was no clear pattern of increase in the incidence of vulval ulceration with age. Female subjects aged 70 or older seem to have a higher incidence of vulval ulceration in comparison with other age groups.
- There was no difference in the incidence rates of vulval ulceration when using clinical codes considered to be more specific for idiopathic vulval ulceration and when including the codes stating a known aetiology. Post-vaccination incidence rates of vulval ulceration were not different than the background incidence rates either 30 or 90 days after receiving the first dose of Comirnaty vaccine, or after receiving the second or third doses. Similar results were obtained for the other COVID-19 vaccines (Spikevax and Vaxzevria). However, confidence intervals of the incidence rates were relatively wide due to a limited number of follow-up years

in each stratum analysed. This implies that the study is lacking power to provide an adequate precision in our estimates.

- The SCCS analyses also found no increase in the incidence rate of vulval ulceration in the period after vaccination.
- The various sensitivity analyses performed support the findings from the main analysis.

6.2.Limitations

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: this is automatically fed back into the GP clinical system. A high level of completeness of recording of COVID-19 vaccination status in GP software is expected, although we are not aware if this has been validated.

Uncertainly about the completeness of the ascertainment of exposure and a high level of uptake of the vaccines at a population level means that a meaningful unexposed cohort cannot be identified, so a comparative analysis against unexposed patients is not possible. For this reason, we have proposed the approach of using a different COVID-19 vaccine as a comparator and using the SCCS study design.

Vulval/vaginal ulceration is rare, and it is not known if it has been validated as an outcome in primary care databases. For this reason, a sensitivity analysis has been proposed to incorporate a wider range of terms. It is possible that mild cases of short duration do not present or get recorded by general practitioners.

7. References

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Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

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

The Health Improvement Network (THIN®) Spain

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. THIN® Spain is globally representative of the whole national demographics and prevalence on the main chronic health pathologies. THIN® Spain includes 3,000,000 individuals out of the overall population. Among these, 1,050,000 are active in the previous year and 1,800,000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals. New patients are automatically included into the database, and deceased patients identified in a specific field.

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

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

Annex 2 – Codelists

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

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® ES

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

Table A3. Codes use to identify outcomes in IMRD UK

Code	Clinical term
primary outcome (narrow definition)	
K42y2	Ulcer of vagina
K425	Ulceration of vulva
K4250	Ulceration of vulva unspecified
K425z	Ulceration of vulva NOS
^ESCTVA300088	Vaginal ulcer
^ESCTVA300090	Vaginal ulceration
sensitivity analysis (broad definition) - codes used in addition to those listed above	
A5412	Herpetic ulceration of vulva
K4251	Ulceration of vulva in diseases EC
K4252	Ulceration of vulva in Behcet's disease
Kyu84	[X]Ulceration of vulva in infectious+parasitic diseases CE
Kyu86	[X]Vulvovaginal ulceration+inflammation in other diseases CE
^ESCTTR552111	Traumatic blister of vulva, infected
^ESCTVA574834	Vaginal blister
related terms excluded	
A992-2	Pudendal ulcer
K4211-1	Vulval sores *
M181-2	Vulva sore †
any codes related to genital herpes	
SD12C	Blister of vulva
SD12D	Blister of vagina
SD13C	Blister of vulva, infected
SD13D	Blister of vagina, infected

* This code stopped being used in 2019-2020 and so was not used following vaccination against COVID-19.

† This code is widely used but seems to be related to vulval pain/pruritis.

Table A4. Codes use to identify outcomes in THIN® ES

Diagnostic code	Clinical term
FUES.CIE9.616.5	ULCERATION OF VULVA
FUES.CIE9.616.50	ULCERATION OF VULVA NOS
FUES.CIE9.616.51	ULCERATION OF THE VULVA IN OTHER DISEASES