14 October 2022

Data analysis plan

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
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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

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 will be 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 will be 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 will be the general female population in the UK and female patients visiting general practices in Spain.

4.3. Data sources

The following in-house databases will be 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 will be identified from the bespoke vaccination data table.

Annex 2 shows the codes that will be used for each database.

Outcome

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

Other variables

Vaccine utilisation will be stratified by age group and number of doses. Event rates for vulval ulceration in the general population will be stratified by age group and year. Event rates among exposed patients will be stratified by age, and number of doses. Age will be 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 will describe 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 will 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 will be required to have a minimum observation time of 365 days prior to entering into each period in order to establish whether events observed during the period are incident (first-ever) cases. Patients will be excluded from the analysis if they have any prior history of any of the selected codes for vulval ulceration in the database. The study period will vary according to the years of coverage in the two databases (UK, and Spain). For IMRD (UK) database, the covered period will be from 2012 to 2019. For THIN® Spain, the covered period will be from 2014 to 2019.

- Numerator: The numerator will consist 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 will be excluded. Included patients will only be able to contribute one event.

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

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

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

Time will be truncated where patients enter or leave the study cohort part way through a time period or where they have an event.

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

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

This will be presented as the number of events per 100,000 person-years and will be 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 will be 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 will be 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 will be followed up for a maximum of 30-day following first exposure, a cut-off subject to sensitivity analyses. Thus, the incidence rate will be calculated as new onset events divided by the total duration of follow-up time in years. Patient will be censored from the analysis if they leave the population (i.e., moved practice, die, or reached the end of follow-up for their practice), or when they are exposed to an alternative COVID-19 vaccine.

Event rates will be stratified by the age groups described above. The primary analysis will consider the 30-day period after the initial vaccine. A secondary analysis will look at the second and subsequent exposures to the vaccine. The covered period will be mainly 2021.

4. Event rates among exposed patients to other COVID-19 vaccines: The same analysis described in (3) will be run with an alternative COVID-19 vaccine used as a comparator. For IMRD (UK) the comparator will be Vaxzervria as this was the second most widely use vaccine in the UK. For THIN® ES, the comparator could either be Moderna (more widely used in Spain, but an RNA vaccine similar to Comirnaty) or Vaxzervria (less widely used in Spain but using a different technology to Comirnaty). To compare event rates between Comirnaty and the comparator vaccine, event rates will be 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 at all age ranges, it seems to be less common in the very young and very old. The covered period will be mainly 2021.

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 will be 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 starts 1-year after first entry onto database.

Event definition: As defined in section 4.4 above. In this analysis, repeated events will be allowed. Events coded within 30 days of a previous coded event (or a string of events within 30 days of each other) will be 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 can be incorporated (n^{th} vaccinations). Pre- and post-initial vaccination "at risk" periods will be evaluated separately (to see if there is any evidence that the effect is not transient) and combined if appropriate.

Assumptions:

- No confounding by age since we are assessing 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.
- Event does not prohibit subsequent vaccination.
- Event is not associated with increased risk of death.
- Event rates are constant within time windows: the outcome event codes are used reasonably consistently between 2019 and 2022.

Methods: We will compare event rates (n events / follow-up time) in not-at-risk "unexposed" 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 will be from 01 Jan 2019 to 31 May 2022.

4.5.3. Sensitivity analysis

For the **main analysis**, sensitivity analyses will include calculating event rates in exposed subjects over 90 days follow-up post vaccination (as opposed to 30 days). In addition, a broader endpoint definition will be used to include vulval/vaginal ulceration of known cause.

For the **explorative analysis** (self-controlled case series), we will estimate 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 – this will make little impact)
- Exclude patients with history of event at start of follow-up
- Test the 30-day cut-off for discrete events
- Exclude patients who do not survive to end of follow-up (31May2022)

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

4.6. Quality control

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

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

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

4.7. 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: 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.

5. Protection of human subjects

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

6. Management and reporting of adverse events/adverse reactions

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

7. Plans for disseminating and communicating study results

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

8. References

1. Huppert JS. Lipschutz ulcers: evaluation and management of acute genital ulcers in women. Dermatol Ther. 2010 Sep-Oct;23(5):533-40.
2. Approach to the patient with genital ulcers. UpToDate. Accessed via https://www.uptodate.com/contents/approach-to-the-patient-with-genital-ulcers on 22/07/2022
3. Eurostat https://ec.europa.eu/eurostat/databrowser/view/demo_pjangroup/default/table?lang=en
4. Whitaker HJ, Farrington CP and Musonda P. Tutorial in Biostatistics: The self-controlled case series method. Statistics in Medicine 2006, 25(10): 1768-1797
5. Petersen I, Douglas I and Whitaker H. Self-controlled case series methods – an alternative to standard epidemiological study designs. British Medical Journal. 2016; 354: i4515

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

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

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

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

Annex 2 – Codelists

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 will not be 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