ASSOCIATION BETWEEN THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME (TTS) OR THROMBOEMBOLIC EVENTS, AND COVID-19 VACCINES: RESULTS FROM OBJECTIVES 1 AND 2

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Research question and objectives	1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **thrombosis with thrombocytopenia syndrome/s (TTS)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors; 1b) To quantify the **comparative association** of developing **TTS** between the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors; 2a) To quantify the association of the administration of a COVID-19 vaccine and the occurrence of **thromboembolic events (TE)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors; 2b) To quantify the comparative association between the occurrence of TE and the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors; 3) To study the **association** between potential **risk factors and TTS/TE** in people receiving COVID-19 vaccine/s; 4) To characterize the **treatments** used in vaccinated patients with **TTS/TE**, including the use of anticoagulants and other therapeutic products; and 5) provide genetic insights into the development of VTE among the vaccinated population
Country(-ies) of study	Italy, France, Germany, Netherlands, Spain, and United Kingdom
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TABLE OF CONTENTS

2 List of abbreviations

Abbreviation	Name
ATE	Arterial thromboembolism
ASMD	Absolute standardised mean difference
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
CPRD	Clinical Practice Research Datalink
CVST	Cerebral venous sinus thrombosis
DA	Disease Analyzer
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EHR	Electronic Health Record
HES APC	Hospital Episode Statistics Admitted Patient Care
HM	Hospital de Madrid
IPCI	Integrated Primary Care Information
IRR	Incidence Rate Ratio
LPD	Longitudinal Patient Data
MACE	MAjor Cardiovascular Events
MDRR	Minimum Detectable Relative Risk
OMOP	Observational Medical Outcomes Partnership
OR	Odd Ratio
PE	Pulmonary Embolism
PS	Propensity Score
RR	Relative Risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SVVT	Splanchnic and Visceral Vein Thrombosis
TTS	Thrombosis with Thrombocytopenia Syndrome/s
TE	Thromboembolic Events
VTE	Venous ThromboEmbolism

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4 Abstract

Rationale and background:

Thrombosis, alone or with thrombocytopenia syndrome (TTS), are being investigated as potential adverse effects for some COVID-19 vaccines. Previous literature on this topic is limited by vaccine brands covered, small sample size, and residual confounding or strong modelling assumptions.

Research question and objectives

The study objectives covered in this report include:
1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **thrombosis with thrombocytopenia syndrome/s (TTS)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors; 1b) To quantify the **comparative association** of developing **TTS** between the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors;
2a) To quantify the association of the administration of a COVID-19 vaccine and the occurrence of venous or arterial **thromboembolic events (VTE or ATE)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors;
2b) To quantify the comparative association between the occurrence of VTE/ATE and the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors;

Study design

International distributed network cohort study using real world data from Europe and the United States of America, mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)

Population

The following study cohorts were defined: 1) Unexposed to COVID-19 vaccination, compared to exposed to 1st or 2nd dose of vaccine with time-varying exposure (Objective 1a and 2a); 2) Exposed to 1st or 2nd dose of different brands of COVID-19 vaccines (Objective 1b and 2b).

Variables

TTS was defined based on the Brighton collaboration and encompasses TE events with concurrent thrombocytopenia within 10 days before/after the TE date. TE events of interests consisted of two broad classes namely venous (VTE) and arterial (ATE). For each outcome, its occurrence within up to 28 days following the index date was identified.

Baseline characteristics were extracted for characterisation purposes and to account for confounding, including all recorded socio-demographics, health conditions, and medicines use.

Data sources

Three primary care European databases (ES, NL, UK), two ambulatory (DE, FR), one US inpatient database (US-HCDM) and one US health claims (USOC) database were analysed.

Study size

From the contributing databases, all the individuals satisfying the eligibility criteria for the study were included.

Data analysis

The study period covered from Dec 2020 (first vaccine users) until the latest data available. LASSO regression was used to estimate exposure-specific propensity scores (PS). PS-matching was then applied to select comparable people in each target-comparator cohort. Diagnostics including power (minimum detectable rate ratio<5), observed residual confounding (any confounder imbalance with SMD>0.1) and systematic error (>20% of negative control outcomes associated with the exposure) were used to rule out unreliable analyses. Where deemed reliable based on diagnostics, we reported incidence rates (IR) of each outcome in the up to 28 days following the index date in each PS matched cohort. Calibrated Incidence Rate Ratio (cIRR) were estimated for each target-comparator-outcome using Poisson models and empirical calibration for systematic error. Meta-analytic IRR were obtained using random effects meta-analysis where I2<0.4. Database-specific IRR are reported otherwise.

Results

Overall, over 4.4 million Vaxzevria, over 10.1 million Comirnaty, more than 4.7 million Spikevax, and over 1 million Janssen vaccine users were identified, with subsets of these PS-matched and included in different numbers in the proposed analyses.

None of the vaccine vs unvaccinated analyses (Objective 1a and 2a) passed diagnostics, due to observed residual imbalances for known confounders and large unresolved systematic error.

After PS matching, comparative safety analyses (Objective 1b and 2b) showed an increased risk of thrombocytopenia among Vaxzevria vs 1-dose Comirnaty vaccinees (meta-analytic cIRR 1.33 [1.18-1.50]), and a potential excess risk of TTS VTE for Janssen vs 1-dose Comirnaty (meta-analytic cIRR 2.26 [0.93-5.52]).

Conclusions

Differences in vaccine uptake and prioritisation of specific subgroups for earlier vaccination led to unresolvable confounding by indication in the planned cohort analyses of vaccinated vs unvaccinated individuals (Objectives 1a and 2a). Other methods including SCCS or historical cohort comparisons might be preferable and have been conducted previously.

Comparative safety analyses (Objectives 1b and 2b) showed a 30% increased risk of thrombocytopenia in those exposed to 1-dose Vaxzevria vs Comirnaty. Similarly, a potential increase in risk of TTS-VTE among Janssen vs 1-dose Comirnaty vaccinees.

5 Amendments and updates

There have been no formal amendments to the report so far.

Number	Date	Amendment or update	Reason
1	*23/03/2022*	*Changes in report text and rewording/editing of style*	*This report was amended following feedback from EMA reviewers*
…			

6 Milestones

Milestone	**Planned date**
Approval Study Protocol by EMA	Aug 2021
<Registration in the EU PAS register>	Aug 2021
Start of data collection	No data collection is required.
End of data collection	No data collection is required.
Draft report	Jan 2022
Final study report accepted by EMA	Feb 2022
Manuscript to be provided to EMA	Feb 2022

7 Rationale and background

As of May 2021, four different COVID-19 vaccines were granted conditional marketing authorisation by the European Medicines Agency (EMA) after showing high efficacy and safety in phase-3 clinical trials [1-3]. These vaccines are classified into either viral vector-based including Vaxzevria (previously AstraZeneca or ChAdOx1) and COVID-19 Vaccine Janssen, or mRNA including Comirnaty (previously BNT162b2) and Spikevax (previously Moderna). After millions of vaccine doses were administered in large-scale immunization campaigns, spontaneous case reports of thrombosis with thrombocytopenia syndrome (TTS) usually within 2 weeks following the first dose of viral vector-based vaccines emerged [4-6]. As of 7th July 2021, 405 reports of major thromboembolic events with concurrent thrombocytopenia had been documented following 44.3 million first doses and 33.9 million second doses of the Vaxzevria vaccine in the UK[7]. Although fewer concerns have been raised about safety signals for Comirnaty (mRNA COVID-19 vaccine), instances of immune thrombocytopenia have also been observed among recipients of this vaccine[8].

A causal relationship was considered possible by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), leading to an update of the respective product information to include TTS as a very rare side effect [link]. As these unusual blood clots in combination with low thrombocyte counts were reported pre-dominantly among women aged <60 years, several European countries restricted the use of viral vector-based vaccines in younger age groups as a pre-cautionary measure. While the pathogenesis is not yet fully understood, an immune response leading to the development of pathologic platelet-activating antibodies is suggested (vaccine-induced immune thrombotic thrombocytopenia)[6, 9]. Although these events are very rare, based on the worldwide roll-out of these vaccines absolute numbers of affected patients may accumulate fast.

To further monitor COVID-19 vaccine safety and complement pharmacovigilance measures, multi-national observational studies have been requested by the EMA. Incidences of patient-reported side effects after COVID-19 vaccination [10] and adverse events of special interest [11, 12] are closely being monitored. The Covid-Vaccine-Monitor [13] project will facilitate the rapid signal assessment of emerging safety concerns. While these studies are designed to identify a broad range of new potential safety signals, one ongoing EMA project already focusses on cardiovascular and thromboembolic risk in both COVID-19 patients and COVID-19 vaccinated people [14]. The study is assessing incidences of thromboembolic events and their consequences, as well as risk factors for thromboembolism in COVID-19 patients and vaccinated people. Background incidence rates of five TTSs of special interest [15] were calculated based on records from over 20 million people in 6 European countries, ranging from 0.1 events per 100,000 person-years for cerebral venous sinus thrombosis/thrombocytopenia to 0.2-4.4 events per 100,000 person-years for stroke/thrombocytopenia. The study found TTS in unvaccinated people to be more common in men and older age groups, which differs from characteristics of the patient group reporting vaccine-related TTS. Preliminary findings from this study also showed larger than expected VTE (predominated by PE) in the 28 days following vaccination with either Vaxzevria or Comirnaty in UK and Spain; increasing rate of thrombocytopenia was seen among people vaccinated with Vaxzevria. In another study based on Danish and Norwegian data, increasing rates of VTE, PE and CVST were also found [16]. More recently, a nested case-control study from Scotland has suggested no increasing risk of VTE with either vaccines [17]. In the light of important public-health decisions being based on TTS-

risk for COVID-19 vaccines in different countries, insight to the magnitude of TTS risk related to COVID-19 vaccination at a large scale is urgently needed.

8 Research question and objectives

The proposed study objectives covered in this report include:

1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **TTS** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.

1b) To quantify the comparative risk of developing TTS among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

2a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **venous or arterial thromboembolic events (VTE or ATE)** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.

2b) To quantify the comparative risk of VTE/ATE among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

9 Research methods

9.1 Study design

We conducted a network cohort study using routinely collected health care data mapped to the OMOP CDM.

9.2 Setting

9.2.1 Countries

Datasets from France, Germany, Netherlands, Spain, United States and United Kingdom informed the analyses (see section 9.4 Data Sources for more details).

9.2.2 Study period

The study period to identify exposure and outcomes covered from Dec 2020 (first vaccine users) until the latest data release available in each of the contributing databases (see Section 9.4).
For each objective and data source the study period was unique and went from cohort-specific index date to the latest data available or 28-day follow-up. Cohort-specific index dates were:

- For vaccinated people (and matched unvaccinated) [*Objectives 1a-2a*]: date of dose vaccine (and same date for matched unvaccinated)
- For comparative cohorts [*Objectives 1b-2b*]: date of first dose of the index vaccine brand

Specific time windows for each of the objectives is specified in Section 9.2.4.

9.2.3 Study cohorts

All adult persons (aged >=18 at the start date of database) registered in any of the contributing databases within the study period and with at least one year of database history before the index date were included in the target population. One year prior history was to ensure a sufficient period to identify health conditions and medication use prior to individuals´ index dates.

- **Study population for Objectives 1a and 2a**: Of people in the target population, those with at least one exposure to any COVID-19 vaccine in the study period were included in the 'exposed' cohort/s, with 1st and 2nd dose vaccine date as time-varying exposure. Time-varying exposure was to avoid immortal time bias [18] and boost sample size for the comparator cohort (unvaccinated). It means that everyone in the database first entered in the study as unvaccinated. Those who received COVID-19 vaccine were also regarded as the partially or fully exposed cohort according to the change of their vaccination status. This approach has recently been used by Barda et al using Israel real world data[19].

Unexposed matched participants were pooled from the target population (as specified in Section 9.2.4).

Three different cohorts, described below, and two different comparisons of exposed and comparator cohorts were built in CPRD (AURUM) and SIDIAP:

1) Persons who received 1st of COVID-19 vaccine (i.e. partially exposed cohort/first dose vaccinated cohort) were compared to those who did not receive any COVID-19 vaccine (comparator cohort).
2) Persons who received 2nd dose of COVID-19 vaccine (i.e. fully exposed cohort/ second dose vaccinated cohort) were compared to those who did not receive any COVID-19 vaccine (comparator).

Study populations for Objective 1b and 2b: Those with exposure to an adenovirus-based COVID-19 vaccine brand were included in the target cohort, and those vaccinated with an mRNA-based COVID-19 vaccine in the active comparator cohort.

In each contributing database, the following different target and comparator cohorts were built for Objectives 1b and 2b where available:

1. 1st dose Vaxzevria* vs 1st dose Comirnaty
2. 2nd dose Vaxzevria* vs 2nd dose Comirnaty
3. 1st Vaxzevria* vs 1st dose Spikevax
4. 2nd Vaxzevria vs 2nd Spikevax
5. 1st COVID-19 Vaccine Janssen vs 1st dose Comirnaty
6. 1st COVID-19 Vaccine Janssen vs 1st dose Spikevax
7. Heterologous vs homologous: heterologous cohorts were built where people had Vaxzevria as the 1st dose followed by Comirnaty or Spikevax as the 2nd dose. These were compared where possible to comparator homologous cohorts where both doses were Vaxzevria. These cohorts were only attempted to build in Spanish, French, and German databases where heterologous vaccine schedule was recommended.

* Vaxzevria is not authorized in US and therefore all comparisons involving it were not conducted using US databases.

*Homologous cohort only included Vaxzevria as COVID-19 Vaccine Janssen was given as a single injection during the study period.

Note: we excluded people who received more than one brand of COVID-19 vaccine on the same date, or who did not have a vaccine brand specified in their records, as these were deemed as potential data errors. In addition, we also excluded people who received their second dose less than 21 days after the first for similar reasons.

9.2.4 Follow-up

9.2.4.1 TE and TTS outcome at risk time (Objective 1a-2b)

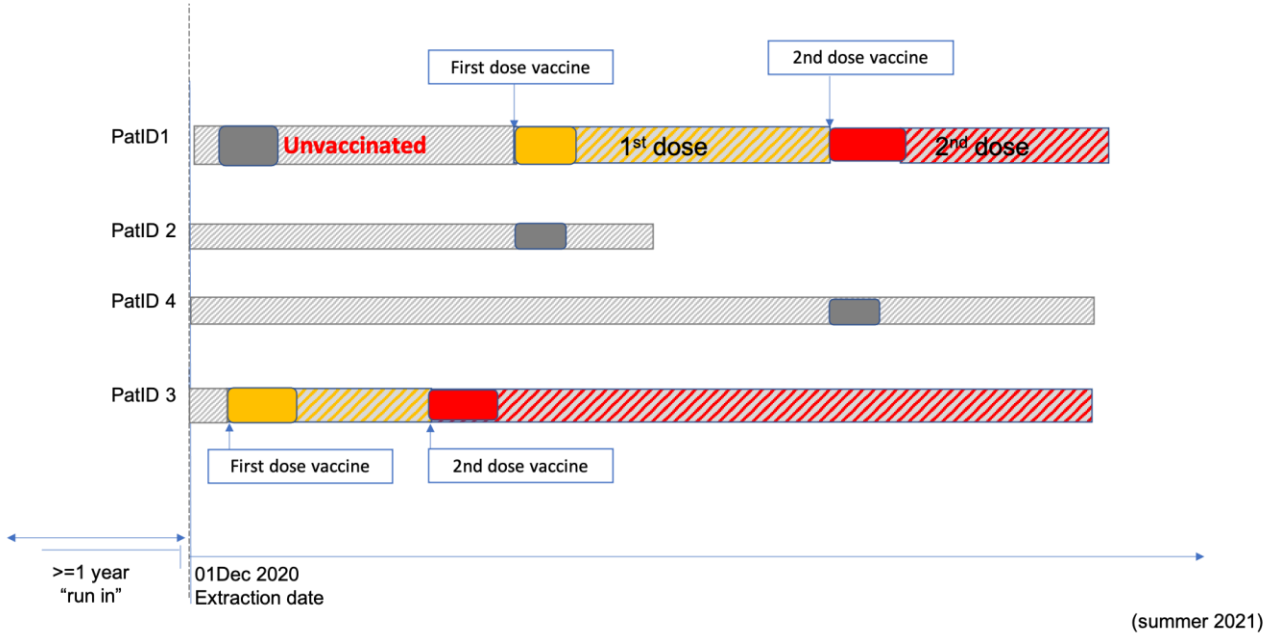
For **Objectives 1a and 2a**, we used time-varying exposures to minimize immortal time bias. This meant that vaccinated persons had multiple index dates depending on their vaccination status during

the study period. Persons were followed until the earliest of the following dates: the last available date, the date of vaccination exposure status change, outcome occurrence, or 28 days after index date. Index dates for this analysis were defined as follows:

- The index date for the second-dose vaccinated cohort was the date when people received their 2nd dose of COVID-19 vaccines, regardless of brand.
- The index date for the unvaccinated was the index date of their matched 'vaccinated' counterpart (see Section 2.7 for detail on the propensity score matching process).
- Additionally, index date for the unvaccinated when compared to second-dose vaccination was the date of second dose vaccination for their PS matched counterpart.

Figure 1 shows an illustrative example of time-varying exposure and follow-up times for each index date using four patients: PatID1 was vaccinated in Mar 2021 with the 1st, had an event 20-days post 1st vaccination, and in June with the 2nd dose, PatID2 was not vaccinated before deceased, PatID3 was vaccinated in Dec 2020 and Mar 2021 with the 1st and 2nd dose, and PatID4 remained unvaccinated throughout the whole study period. In this graph, the outcome at risk time window (28 days) is shown with solid bars and the time outside the outcome at risk window are shown by bars with diagonal stripes.

Figure 1. Diagram of study follow-up for Objective 1a-2a



For vaccinated people, like PatID1 and PatID3, the follow-up time in the 'first dose vaccinated cohort' and in the 'second dose vaccinated cohort' for VTE/ATE/TTS started from the date of 1st and 2nd

vaccination respectively, and ended with either the earliest of the 28-day or last available date or the 2nd vaccination date (only for 1st vaccination), as illustrated with solid yellow (1st vaccination) and solid red (2nd vaccination) bars for PatID1 and PatID3. The dates of 1st and 2nd vaccination were their index dates.

PatID-2 was unvaccinated before deceased though had similar baseline characteristics at the date of first vaccination of PatID1, indicating similar probability of vaccination within the given calendar period to PatID1. Through the propensity-score-matching exercise for the comparison between unvaccinated vs vaccinated, PatID2 was propensity score-matched to PatID1. To avoid surveillance bias, PatID2's follow-up started with the index date of the matched 'vaccinated' counterpart PatID1 and ended 28 days later, as shown by the solid grey bar. Likewise, in the same propensity-score-matched exercise, PatID1's unvaccinated time was propensity-score-matched to PatID3 who was vaccinated earlier and therefore, was assigned to the index date of PatID3's 1st vaccination date and was followed up 28 days following that index date, as shown by grey bars for PatID1.

In another propensity-score-matching exercise for the comparison between 2nd vaccination vs unvaccinated, PatID4 was propensity-score-matched to PatID1 and the follow-up for that analysis was 28 days from PatID1's second vaccination date.

Follow-up for **Objectives 1b and 2b** started from the index date of 1st vaccination date of the index vaccine, and continued until the earliest of the following dates: the last available date, the date of second dose vaccination, outcome occurrence, or 28 days after index date.

9.3 Variables

9.3.1 Exposures-vaccination against SARS-CoV-2

Each vaccine brand was defined based on standard concepts in the OMOP Common Data Model (CDM) vocabularies. An R cohort diagnostic package was written and was updated and used to identify "orphan source codes", then included in definitions/algorithms for the identification of COVID vaccine exposure/s across participating databases. The analysis package provided the final exposure cohort definitions, concept sets and associated source codes. Exposure cohorts were built as described in Section 9.2.3.

9.3.2 Study outcomes

9.3.2.1 Thromboembolism (TE)

The following thromboembolic events (TE) of interest, preliminary code list shown in Annex 4, were studied:

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE) as a composite of DVT or PE
- Cerebral venous sinus thrombosis (CVST)
- Splanchnic and visceral vein thrombosis (SVT)
- Ischemic stroke
- Myocardial infarction
- Arterial thromboembolism (ATE) as a composite of the two above

9.3.2.2 TE and thrombosis with thrombocytopenia syndrome (TTS)

Our definition of TTS, the primary outcome for Objectives 1a and 1b, was based on the one proposed by the Brighton collaboration (**link**), and encompassed the occurrence of one of the TE of interest above (9.3.2.1) with concurrent thrombocytopenia, identified within 10 days before/after the thromboembolic event date after the vaccination.

Thrombocytopenia was identified either by a diagnostic code or a measurement of <150,000 platelets per microliter of blood as proposed by the Brighton collaboration, observed over a time window post vaccination starting ten days prior to the event of interest and up to ten days afterwards. This definition has been implemented in the OMOP CDM as part of our ongoing study [20].

The following additional definitions were used for sensitivity analyses in Objectives 1a and 1b:

- TTS with recent/closer thrombocytopenia: by reducing the time window to 5 days before/after thrombosis post vaccination
- TTS with severe thrombocytopenia: by reducing the threshold to <100,000 platelets per microliter for the definition of thrombocytopenia based on laboratory data

We analyzed TTS as the combination of thrombocytopenia with each different TE event, as well as a composite 'Any TTS' (any thrombosis with thrombocytopenia), and TTS ATE and TTS VTE. TTS ATE included the combination of myocardial infarction or ischemic stroke with thrombocytopenia as detailed above. TTS VTE included DVT or PE combined with thrombocytopenia.

9.3.2.3 Negative controls

Negative controls were outcomes that were not expected to be causally associated with vaccine exposure. We used 92 negative control outcomes previously used for vaccine safety research[21] in this study. These were pre-specified based on clinical knowledge and previous literature, validated by two clinicians/clinical epidemiologists, and tested in previous work on other vaccine safety projects[22, 23].

Table 1 below shows the concept id for these negative control outcomes. In each database, only negative control outcome with at least 5 counts were included in the negative control calibration analysis.

Table 1. Negative control outcomes: list of included concepts.

Concept Id	Outcome Name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis

Concept Id	Outcome Name
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung’s disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism

Concept Id	Outcome Name
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud's disease
37018294	Residual osteitis
4288241	Salmonella 23tilizat subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor's bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets

9.3.2.4 Covariates

Baseline covariates included in the propensity score (Objective 1 and 2) were extracted using feature extraction package. In short, condition groups and drug era groups as well as demographics (age in 10-year bands and biologic sex) were generated.

We defined baseline covariates based on information prior to the index date:

- Demographics
  - Age group (10-year bands)
  - Sex
  - Index year
  - Index month
- Past medical history observed anytime prior to cohort index
- Medicines use identified based on concept or any its descendants observed during 180 days to 4 days prior to cohort index
- Procedure/s recorded as concept or any its descendants observed during 180 days to 4 days prior to cohort index
- Measurement record for the verbatim concept observed during 180 days to 4 days prior to cohort index
- Composite comorbidity and thrombosis risk indices:
  - Charlson Index, Romano adaptation[24], based on records any time prior to cohort index
  - CHA2DS2-VASc (Congestive heart failure hypertension- vascular disease)[25], based on conditions recorded any time prior to cohort index
- Summary counts of drugs/procedures/visits/observations/measurements
  - Number of distinct drugs observed in 180 days to 4 days prior to cohort index (defined as unique RxNorm ingredient concepts)
  - Number of distinct procedures observed in 180 days to 4 days prior to cohort index (defined as unique SNOMED concepts)
  - Number of distinct observations observed in 180 days to 4 days prior to cohort index
  - Number of distinct measurements observed in 180 days to 4 days prior to cohort index (defined as unique SNOMED concepts)
  - Number of visits observed in 180 days to 4 days prior to cohort index

9.4 Data sources

Data access for Objectives 1-2 was planned to include five European primary care and two ambulatory/outpatient specialist databases. In addition, one US health claims and one large US hospital database was accessed to maximize sample size and exposure to vaccines currently under-represented in European data e.g. Janssen and Spikevax. A summary of key features of the proposed data sources is reported in Table 2.

Table 2. Planned contributing databases. Note that cells shaded in grey highlight data sources that could not contribute to analyses for the reasons explained in the text below

Database	Country	Active Size (2021)	Planned analysis contributions	Key data available				
				COVID vaccine/s	Hospital treatments	Hospital outcome/s	Outpatient treatments	Plate-let counts
CPRD GOLD	UK	3.2m [26]	1b, 2b	I	No	I	Yes	Yes

CPRD AURUM	UK	13m [27]	1a,1b,2a,2b	C	No	I	Yes	Yes
RCGP RSC	UK	17m	1a,1b,2a,2b	C	No	I	Yes	Yes
SIDIAP with CMBD	ES	6m	1a,1b,1,2a,2b	C	No	Linked	Yes	Yes
IPCI	NL	2m	1b*,2b*	I	No	I	Yes	Yes
LPD France	FR	2.3m	None (Obj 3-4)	I	No	I	Yes	Yes
DA Germany	DE	8.5m	1b*,2b*	I	No	I	Yes	Yes
OpenClaims	US	187m	1b*,2b*	I	I	I	Yes	Yes
Hospital CDM	US	30m	1b*,2b*	I	Yes	Yes	I	I
Parc Salut Mar	ES	1m	None (Obj 3-4)	I	Yes	Yes	No	No

Specifically, for the countries where general practitioners act as gatekeepers to the system, primary care databases are best positioned to identify COVID-19 vaccines. This included CPRD GOLD (UK), CPRD AURUM (UK), RCGP RSC (UK), IPCI (NL) and SIDIAP (ES). For countries where general practitioners do not act as gatekeepers to the system (France and Germany), outpatient records (IQVIA DA France and Germany) including general practice and ambulatory specialist data were used to identify vaccine exposure, with expected incompleteness of vaccine records.

After study initiation, we learned that vaccine exposure would become complete (fully recorded through linkage in origin or at the data processing stage) for **CPRD AURUM, GOLD, and SIDIAP**. These were therefore the primary sources planned for analyses of **Objectives 1a &2a** to avoid exposure misclassification in the 'unvaccinated' cohort and time-varying exposure.

In all other data sources, exposure to vaccines was incomplete because vaccine exposure information was not embedded into the system but can be obtained through a linkage to the databases, often with a delay in timing. This meant lack of vaccine records did not imply unvaccinated status. However, the presence of a vaccine record was assumed equivalent to vaccine administration. Therefore, these data sources only contributed to the analysis of comparative safety (Objectives 1b and 2b).

LPD France and Parc Salut Mar were not planned for analyses in Objectives 1 and 2 due to uncertainties around vaccine exposure (see initial protocol). This was confirmed for Parc Salut Mar, but LPD France had sufficient exposure to attempt analyses for Objectives 1b and 2b. The latter was therefore included with a caveat due to challenges with the coding of venous thromboembolism (VTE) in this data source previously reported as part of our previous study[15].

SIDIAP was fully linked to CMBD (*Conjunt Minim Basic de Dades a l'Alta Hospitalaria*), hospital data, and provided richer information on inpatient outcomes. Conversely, in CPRD GOLD and

AURUM, linked hospital admissions data was not available on time to cover the necessary study period. Therefore, we were not able to do additional analyses using linked inpatient data.

RCGP did not complete the mapping and data quality checks on time for analyses, and was therefore excluded from this report. Similarly, CPRD GOLD was not available on time, and will be proposed for inclusion in further iterations of this report and/or the related manuscript as results are made available.

9.5 Study size

For each database, all individuals that satisfied the eligibility criteria for any of the listed study cohorts were included.

9.6 Data management

The databases used in this study have been standardised to the OMOP CDM. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system has been harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel/ and in The Book of OHDSI: http://book.ohdsi.org

Analytical code for this study was written using R. Each data partner executed the study code against their database containing previously OMOP-mapped patient-level data, and then returned the results to the lead investigators, only containing aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for the present study report.

9.7 Data analysis

9.7.1 Cohort Diagnostics and Cohort characterization

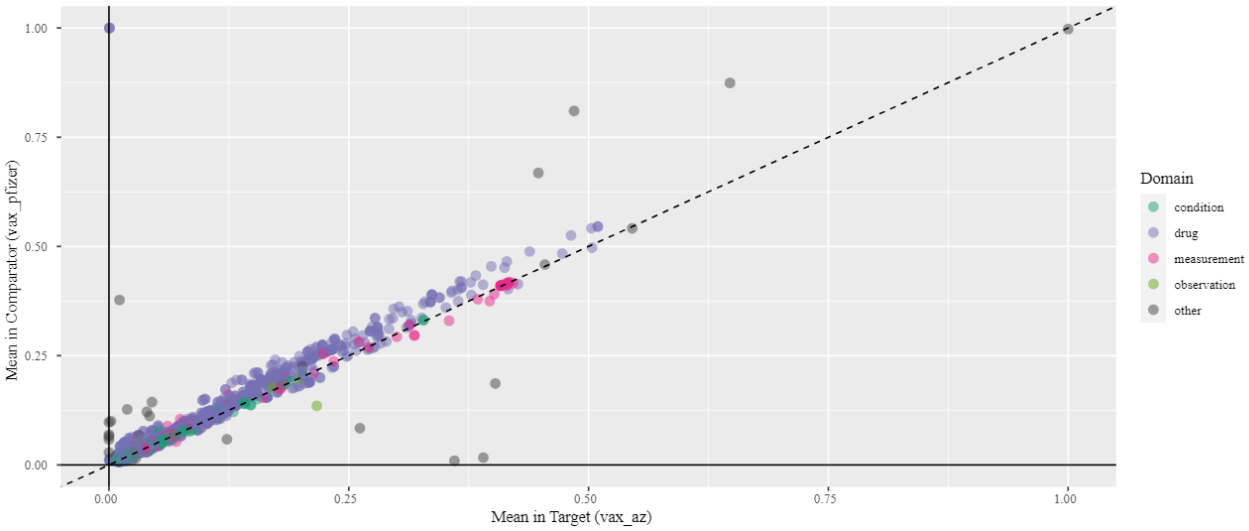
Cohort diagnostics was used to check the consistency in source and mapped coding of vaccine exposures for all databases. A separate cohort diagnostics package was developed to characterize coding of study outcomes, which run previously in all European databases, and was further run in the US-based data sources.

Cohort diagnostics included information on the following:

- Cohort counts for each generated cohort in each database
- Age, sex, and calendar year-specific incidence rates of vaccine exposure/outcome
- Time distributions, including information on observation time available before and after index date, as defined by vaccine exposure or recording of study outcome

- Included concepts, and orphan (potentially missed) concepts/codes
- Index event breakdown, listing concept IDs leading to inclusion in each cohort
- Visit context, describing health care setting where the exposure or event was recorded
- Cohort characterization, providing baseline (pre-index) patient features
- Temporal characterization, providing patient features as recorded in different time windows before, on, and after index date
- Cohort overlap, providing counts of subjects pertaining to 2 or more of the proposed cohorts
- Compare cohort characteristics, providing baseline features for 2 or more cohorts, and a visualization of differences in prevalence of use/history of conditions, medicine/s use, device/s use, procedure/s, and measurements in the "target" (x axis) vs "comparator" cohort (y axis) [see Figure 2 for an example]

Figure 2. Baseline characteristics of two vaccinated cohorts. The comparison of Vaxzevria (x axis) and Comirnaty (y axis) in the SIDIAP database is depicted here as an example



9.7.2 Propensity score estimation and matching

Objectives 1a&2a were addressed using two CPRD AURUM and SIDIAP databases, where each vaccinated (target) cohort was matched to an unvaccinated (comparator) one.

Objectives 1b&2b (comparative safety) were addressed in all contributing databases, where each cohort of people vaccinated with an adenovirus-based vaccine (Vaxzevria or Janssen) "target" cohort was matched to subjects vaccinated with either mRNA vaccine (Comirnaty or Spikevax) as an active "comparator" cohort.

The following steps were applied for propensity score estimation and subsequent matching of target and comparator cohorts:

1. Large-scale propensity scores (PS) were estimated using all covariate information and available for the contributing patients [28]. Lasso regression was used to estimate the probability of belonging to each target cohort according to all covariates for each database-target-comparator combination. This data-driven approach to PS estimation (so called L_1-regularization) has been widely used in previous studies and described elsewhere in detail [29]. During the regularization process, coefficients of covariates that were seen not related to the vaccine exposure were shrunk to zero. A simulation study by Tian et al[29] found that large-scale PS estimation improved the performance of the resulting model compared to clinically-driven PS estimation.

2. The resulting PS models were manually checked by a senior clinical epidemiologist (Prof DPA) to identify any strong instrumental variables. When this happened, a new Lasso model was fitted to estimate an alternative PS after the manual exclusion of the identified instrument/s. Examples of such instruments included certain calendar months (eg December 2020 predicted Comirnaty perfectly, as this was the only vaccine approved on that date), and variables directly leading to vaccine exposure, like codes associated with the invitation to attend a vaccination appointment. This process was repeated until no strong instrument was identified in the resulting PS.

3. Each person in the target cohort was matched to 1 (Objectives 1a/2a) or up to 4 (Objectives 1b/2b) people from the comparator cohort without replacement using greedy matching with a maximum caliper width of 0.2 standard deviations of the logit of the PS [30]. For Objectives 1a/2a, both vaccinated and unvaccinated peers started their follow-up from the same calendar date (i.e. index date of vaccinated people) after matching was completed.

9.7.3 Diagnostics

As pre-specified in our study protocol, three diagnostics were used for each database-specific combination of target-comparator-outcome:

- Statistical power: No analyses were be conducted where the MDRR was >5. In such cases, incidence rates were reported, but no treatment effect estimate is provided.
- Covariate balance: To identify residual (observed) confounding, we explored and depicted covariate balance for all recorded variables in the patient record when comparing target and comparator cohorts before vs after PS matching. Any covariates with a significant imbalance, defined as ASMD>0.1 after matching, was inspected by a senior clinical epidemiologist (Prof DPA). As pre-specified in our protocol, the presence of such imbalances, where identified as suggestive of confounding, resulted in the specific analyses affected not being reported.
- Systematic error: Finally, many negative control outcomes were analysed, and their association with target vs comparator cohort status reported. We pre-specified that treatment effect estimates where >20% of the negative control outcomes remained associated with the exposure of interest after propensity score matching would be highlighted as a failed diagnostic. Empirical calibration was used to minimise the impact of such systematic error, which potentially encompasses residual confounding due to observed and unobserved variables. Treatment effect estimates (IRR) where the systematic error diagnostic failed are reported, but are highlighted in our Results section as they should be interpreted with caution, and only the calibrated IRR (cIRR) should be cited.

9.7.4 Outcome/s modelling

Outcome modelling was conducted and is reported only for the database-target-comparator-outcome combinations that passed statistical power and covariate balance diagnostics.
First, Poisson regression was used to estimate incidence rates (IR) of each of the study outcomes in the up to 28-day period following exposure stratified by target vs comparator cohort status within the PS-matched cohorts.

Secondly, incidence rate ratios (IRR) were calculated based on the proportion of events observed during person-time, according to target vs comparator exposure. No estimates of incidence rate ratios were reported where the minimum detectable rate ratio (MDRR) for a database-target-comparator-outcome combination was >5, as this was deemed too underpowered and therefore unreliable (see Section 9.7.3).

For each of the conducted analyses, we used empirical calibration to account for residual systematic error. This approach has been used in many previous studies in different clinical areas, including comparative effectiveness of osteoporosis medications[31], anticoagulants, or antidepressants [32]. Empirical calibration has also been used in several safety studies related to COVID-19 repurposed therapies [33, 34] [35, 36]. Recently, this method has been acknowledged in the latest version of the EnCePP guide on methodological standards in pharmacoepidemiology [37].

Empirical calibration was therefore used to estimate calibrated IRR whilst taking into account systematic error due to potentially unobserved confounding [38]. Calibrated p-value and effect size: Traditional null hypothesis testing replies on a theoretical null distribution that is only unknown, calibrated significance testing first fits empirical null distributions from negative controls' estimates. Using these distributions, we computed calibrated p-values that reflect the probability of observing the effect estimates under the empirical null hypothesis, taking both random and systematic error of each estimate into account [39]. Apart from calibrated p-value, we also calculated calibrated Confidence Intervals for the IRR.

Both uncalibrated (Step 3) and calibrated IRR and 95% Confidence Intervals were estimated and are reported where statistical power and covariate balance diagnostics passed. IRRs in the presence of substantial systematic error should be interpreted cautiously, and therefore calibrated IRRs are highlighted when this diagnostic failed (see Section 9.7.3).

9.7.5 Database-specific results and pooling

Meta-analysis using random effects models based on the Dersimonian-Laird estimator were obtained where heterogeneity for a specific database-target-comparator-outcome combination showed an I2 of less than or equal to 40%. Database-specific IRRs are reported otherwise. Only treatment effect estimates that passed the covariate balance diagnostic were included for meta-analysis, regardless of power and systematic error. This is because underpowered analyses will still contribute to meta-analytic estimates when pooled.

9.7.6 Sensitivity analyses

The following additional definitions of TTS were used for Objective 1a and 1b:

- TTS with recent thrombocytopenia: reducing the time window to 5 days before/after thrombosis
- TTS with severe thrombocytopenia: by reducing the threshold to <100,000 platelets per

microliter for the definition of thrombocytopenia based on laboratory data

Additionally, a broad definition of stroke called *overall stroke* was used as a study outcome, which included non-specific, haemorrhagic and ischemic stroke was as a sensitivity analysis.

9.7.7 Post-hoc analyses

A post-hoc analytical strategy was tried for the analyses in Objectives 1a and 2a after reviewing the results of the study diagnostics: all steps from PS estimation to outcome modelling were repeated after stratifying by index month (before vs after April 2021) and by age (<40 vs >=40 years old at date of first dose vaccination).

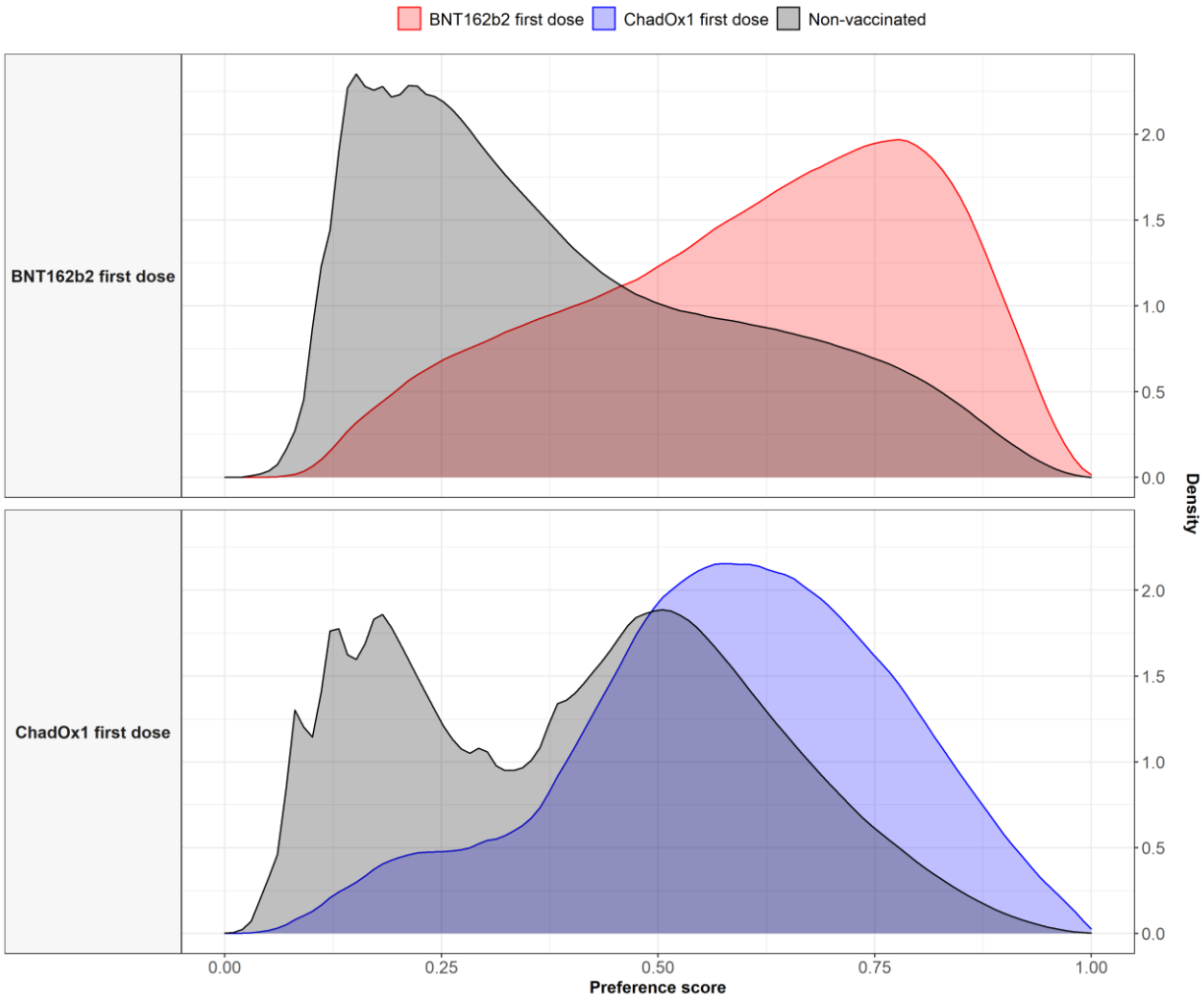
10 Results of Objective 1a and 2a

10.1 Results from CPRD AURUM UK

In CPRD AURUM, a total of 3,781,035 subjects received at least 1 dose of Vaxzevria, 1,834,237 a dose of Comirnaty, and 9,770,278 people contributed to the unvaccinated pool, either partially (becoming vaccinated later in the year) or fully (never vaccinated during the study period). These figures are based on the analysis of 'venous thromboembolism' for illustration, and vary very slightly for other outcomes due to the imposed washout and outcome-specific exclusions.

Propensity scores were estimated, and subjects matched upon using the strategy described above. After this, a total of 1,574,828 people receiving 1-dose Vaxzevria (41.7% of the total available) were matched to 1,574,828 unvaccinated on the same index date. With the proposed follow-up (up to 28 days post-index), they added up to a total of 117,259 exposed and 95,321 unexposed person-years of follow-up respectively. Similarly, 1,007,591 (55.0%) Comirnaty 1-dose vaccinees were matched to the same number of unvaccinated people. The distribution of the preference score (a transformation of the propensity score to show empirical equipoise) in exposed and unexposed after propensity score matching is depicted in Figure 3. It can be seen that even after propensity score matching, the distribution of preference scores of the exposed (red/blue) and the unvaccinated (grey) still differ substantially.

Figure 3. Kernel Density plots of preference scores for vaccinated (red for Comirnaty, blue for Vaxzevria) and unvaccinated (grey) after propensity score mtching



The top key predictors of exposure to Vaxzevria included in the PS model included (in order of coefficient value):

- Count of distinct procedures recorded in the previous 6 months
- Count of distinct observations recorded in the previous 6 months
- Count of measurements recorded in the previous 6 months
- Age

The top key predictors of exposure to Comirnaty included in the PS model included (in order of coefficient value):

- Count of distinct procedures recorded in the previous 6 months
- Charlson comorbidity index
- Number of medicines prescribed/dispensed in the previous 6 months
- CHADS2Vasc thrombosis risk index

Previous COVID-19 infection was amongst the top 15 predictors in both PS models, in both cases positively associated with a higher probability of vaccination. A number of iterations where necessary before estimating these final versions of the PS, where instrumental variables such as "invite for vaccination" or perfectly predictive calendar time (eg "December 2020") were removed before re-estimating the PS. This last version was considered an optimal PS after review, as it includes hundreds of confounders, and no perceived strong or highly predictive instrumental variables. The full logistic model equation, including hundreds of covariates, is available for inspection in our interactive web application (here) under the 'Propensity model' tab.

Despite the comprehensive model for estimating PS , the PS-matching process did not reduce confounding adequately enough, as demonstrated by the presence of residual observed confounding post-matching: Figure 4 depicts imbalances after matching, with each of the dots with an Y axis value above the pre-specified threshold (SMD>0.1) available for review in our interactive web app, under the 'Balance table' tab.

Figure 4. Observed covariate imbalance before (X axis) and after PS matching (Y axis)

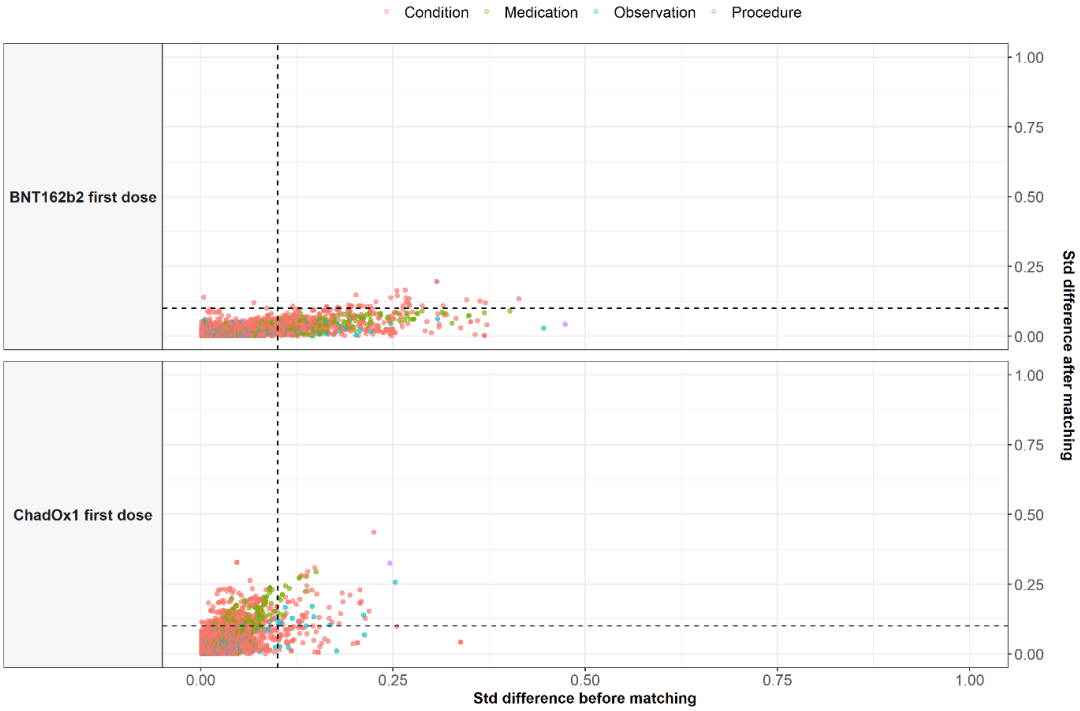


Table 3 shows a summary of strong confounders identified after review of all the imbalanced covariates in the Balance Table. Some of the identified confounders were associated with vaccination strategies and guidelines. For example, age had a U-shape association, with younger ages (<70) more common in the unvaccinated (negative SMD values), and older ones (80 or above) more common in the vaccinated group (positive SMD value). Similarly, comorbidity and frailty were more common amongst the vaccinated. Key strong confounders included predictors of both vaccination and our study outcomes, including dementia/cognitive impairment, chronic kidney disease, atrial fibrillation, heart disease, hypertension, or hyperlipidaemia. This finding of unresolved confounding based on observed covariates was sufficient to consider any further analyses inappropriate based on our pre-specified 'covariate balance' diagnostic.

Table 3. Key identified unresolved confounders with post-matching SMD>0.1

Cohort	Covariate name	SMD
Key confounders after matching Comirnaty 1-dose & Unvaccinated		
1st dose Comirnaty	age group: 40 - 49	-0.113
1st dose Comirnaty	age group: 50 - 59	-0.11
1st dose Comirnaty	age group: 60 - 69	-0.179
1st dose Comirnaty	age group: 80 - 89	0.33
1st dose Comirnaty	age group: 90 - 99	0.136
1st dose Comirnaty	CHADS2VASc	0.24
1st dose Comirnaty	Charlson index - Romano adaptation	0.138
1st dose Comirnaty	History of Atrial fibrillation	0.109
1st dose Comirnaty	History of Chronic kidney disease	0.137
1st dose Comirnaty	History of Essential hypertension	0.119
1st dose Comirnaty	History of Malignant neoplastic disease	0.114
1st dose Comirnaty	History of Mild frailty	0.106
1st dose Comirnaty	History of Moderate frailty	0.148
1st dose Comirnaty	History of Severe frailty	0.107
Key confounders after matching Vaxzevria 1-dose & Unvaccinated		
1st dose Vaxzevria	age group: 40 - 49	-0.351
1st dose Vaxzevria	age group: 50 - 59	-0.24
1st dose Vaxzevria	age group: 60 - 69	0.139
1st dose Vaxzevria	age group: 70 - 79	0.49
1st dose Vaxzevria	age group: 80 - 89	0.28
1st dose Vaxzevria	age group: 90 - 99	0.146
1st dose Vaxzevria	CHADS2VASc	0.574
1st dose Vaxzevria	Charlson index - Romano adaptation	0.364
1st dose Vaxzevria	History of Abnormal pulse	0.151
1st dose Vaxzevria	History of Acute exacerbation of chronic obstructive airways disease	0.118
1st dose Vaxzevria	History of Acute ischemic heart disease	0.123
1st dose Vaxzevria	History of Atrial fibrillation	0.184
1st dose Vaxzevria	History of Cerebrovascular accident	0.102
1st dose Vaxzevria	History of Chronic kidney disease	0.233
1st dose Vaxzevria	History of Chronic obstructive lung disease	0.16
1st dose Vaxzevria	History of Complication due to diabetes mellitus	0.137
1st dose Vaxzevria	History of Dementia	0.117

1st dose Vaxzevria	History of: ECG: atrial fibrillation	0.102
1st dose Vaxzevria	History of Essential hypertension	0.279
1st dose Vaxzevria	History of Frailty	0.328
1st dose Vaxzevria	History of Impaired mobility	0.111
1st dose Vaxzevria	History of Increased lipid	0.186

In addition, systematic error was also thoroughly investigated and inspected in CPRD AURUM after PS-matching both Comirnaty and Vaxzevria exposed to unexposed subjects. In line with the observed confounding detected above, our analysis of negative control outcomes also suggested the presence of systematic error potentially including unresolved confounding.

Figure 5. Systematic error, as defined by the % of negative control outcomes associated with Comirnaty (top) and Vaxzevria (bottom) vaccine exposure

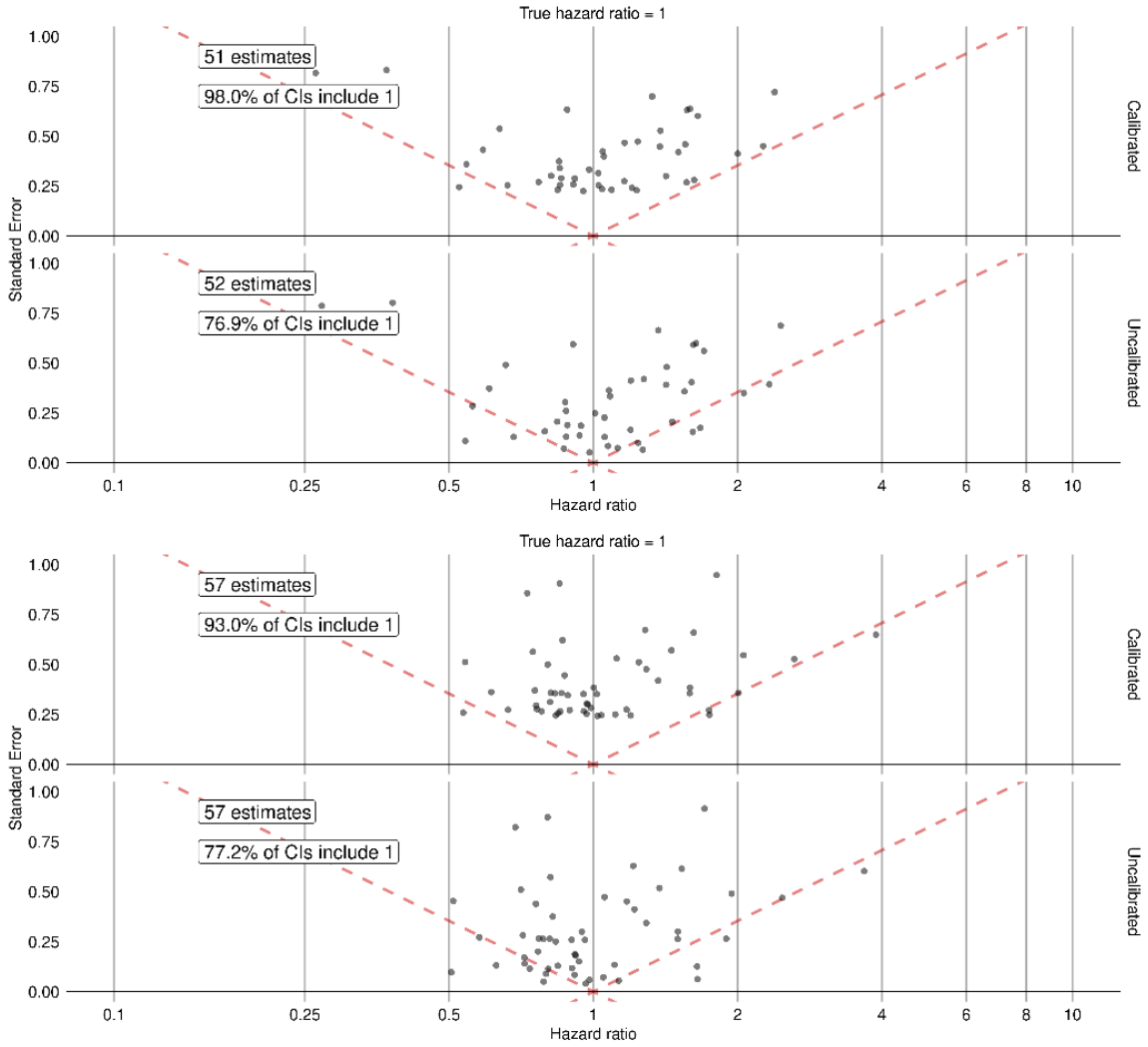
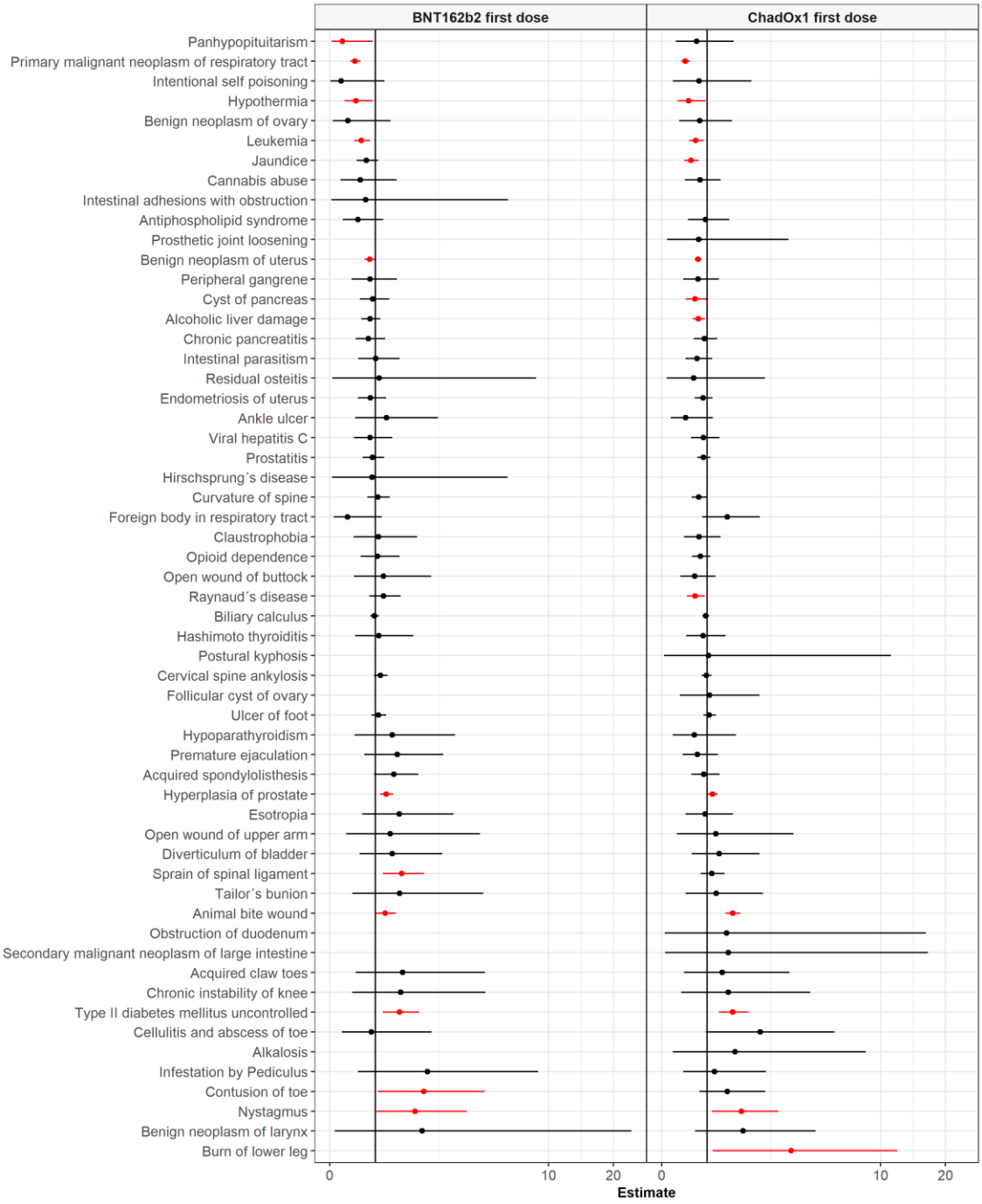


Figure 5 shows the proportion of negative control outcomes associated with vaccination in the PS-matched cohorts. The % with a significant association was over the pre-specified threshold of 20% in both cases, with only 76.9% of negative control outcome analyses including the null (not associated) for the Comirnaty 1-dose exposure, and 77.2% of the equivalent analyses including the null in their confidence interval (not associated) for the Vaxzevria 1-dose analysis. Figure 6 shows one by one the association between vaccine exposure and negative control outcomes.

Figure 6. Systematic error analysis in detail: IRR (95%CI) of each individual negative control outcome and exposure



As shown, a substantial (>20%) of the fitted negative control outcomes were associated (either negatively or positively) with either vaccine exposure. This was additional evidence that any further analyses of the PS-matched cohorts would yield biased estimates. We therefore did not complete any further analytics for Objective 1a-2a in CPRD AURUM.

10.2 Results from SIDIAP-CMBD ES

Over 1.9 million subjects exposed to Comirnaty, over 240,000 exposed to Spikevax, almost 600,000 exposed to Vaxzevria, and almost 125,000 users of Janssen COVID-19 were available for analysis.

Propensity scores were fitted using Lasso regression, and considered adequate excluding strong instrumental variables. Key predictors of exposure to vaccines were similar to those found for CPRD, including age, comorbidity, and medicine/s use.

Models to estimate propensity scores failed for Vaxevria due to high correlation between covariates , particularly age: Spanish vaccination vaccines mandated use of Vaxevria for key workers age <65 until March, and for people aged 60-70 from then onwards (see Figure 7a). The proposed post-hoc analyses (stratification by age < vs >=40 and by index month before vs from April) did not help.

For the other 3 vaccine cohorts (Comirnaty, Spikevax, and Janssen COVID-19), PS models were estimated and used to identify the most similar groups of unvaccinated people to be compared with each vaccinated cohort. However, this strategy failed to balance for confounding: inspection of covariate balance after matching yielded similar findings to those from the UK, with many variables imbalanced as depicted in Figure 7b. Hundreds of covariates remained imbalanced beyond the pre-specified threshold of SMD>0.1 shown as a dash horizontal line in Figure 7b.

Figure 7. Age distribution of people vaccinated with 1-dose Vaxevria vs Comirnaty as identified in SIDIAP-CMBD-ES (top, Figure 7a). Covariate imbalance before (x axis) and after PS matching (y axis) users vs non-users of 1-dose Comirnaty (bottom, Figure 7b)

Figure 7a. Age distribution of people vaccinated with 1-dose (left), 2-dose (middle) Comirnaty/BNT162b2, and those vaccinated with 1-dose Vaxevria/ChAdOx1 (right)

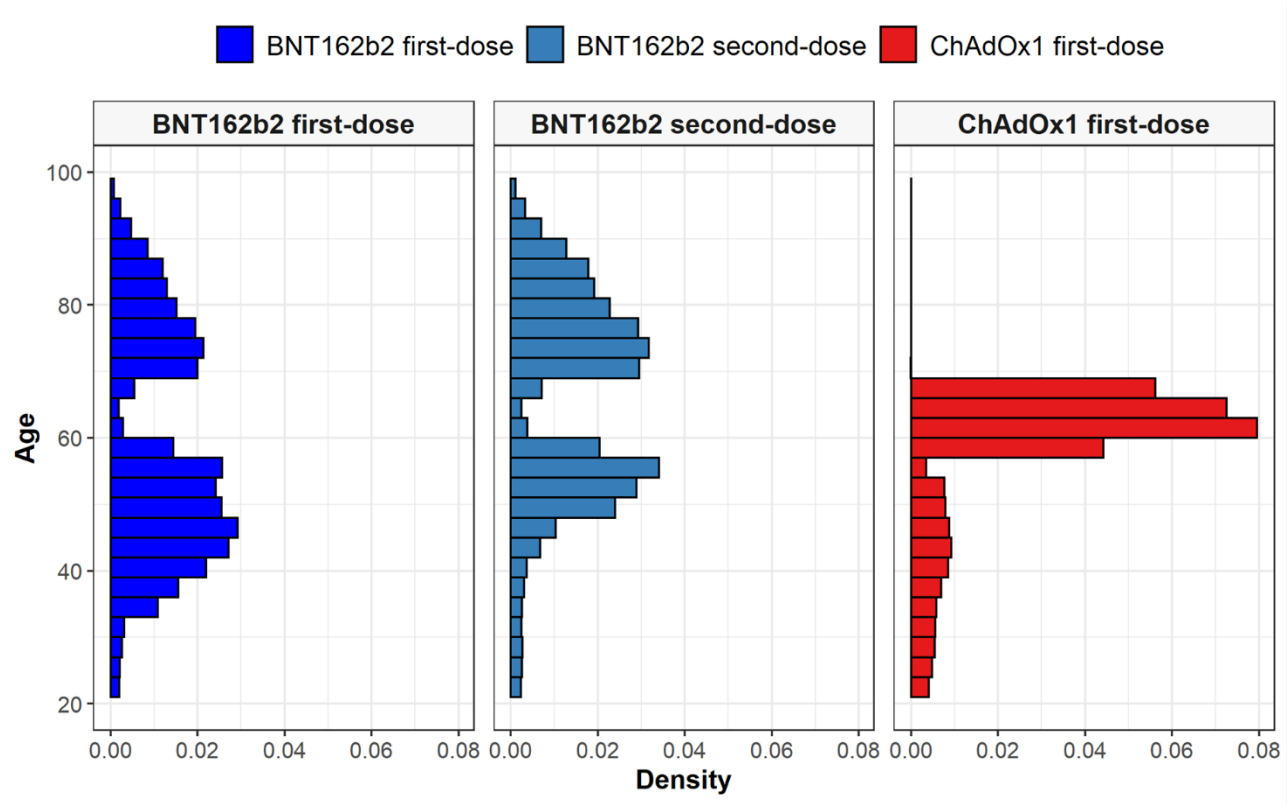
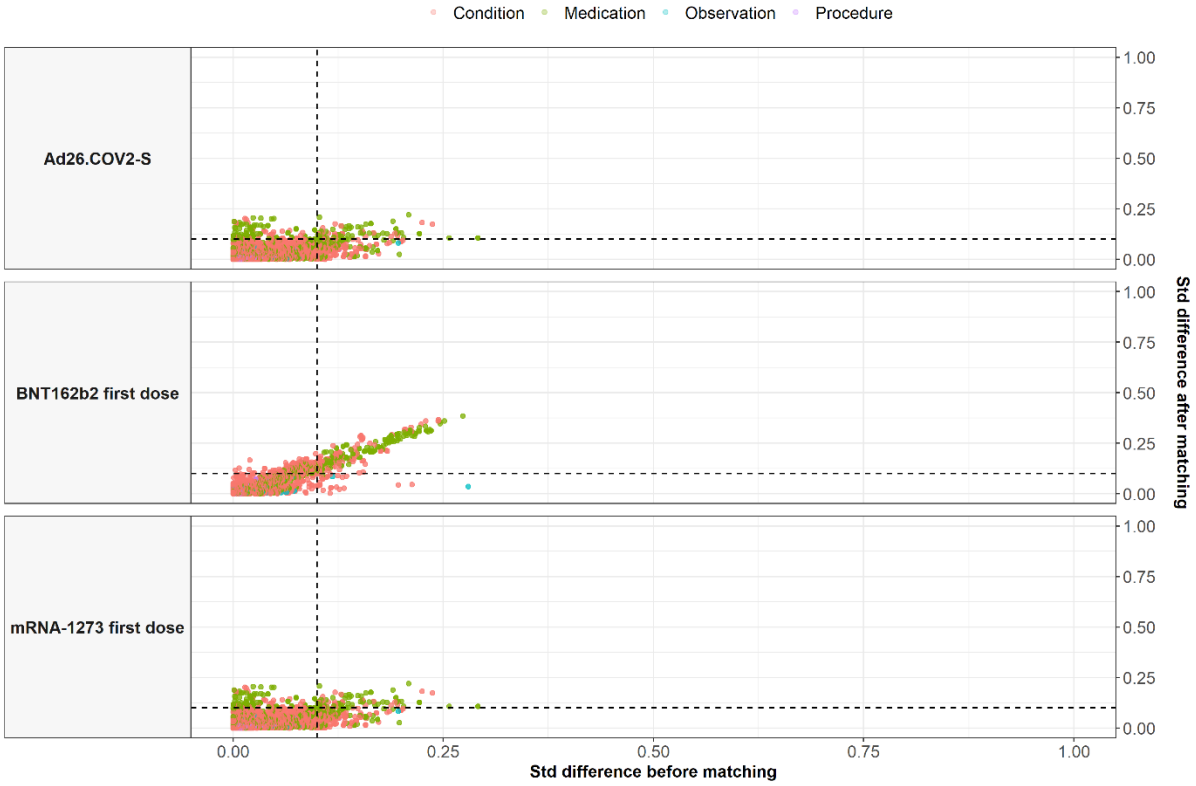


Figure 7b. Covariate imbalance before (x axis) vs after PS matching (y axis) people vaccinated with Janssen COVID-19/Ad26COV2S, Comirnaty 1-dose/BNT162b2, and Spikevax 1-dose/mRNA-1273. Any dot above the pre-specified threshold (horizontal dash line) was inspected to identify key residual confounders



Multiple potentially relevant confounders were identified after manual review of the imbalanced covariates. A list of key confounders is provided in Table 4 as an example. The list includes similar confounders to those seen in Section 10.1: age, Charlson comorbidity index, or CHADS2Vasc thrombosis risk score. The situation was very similar for the Spikevax and Janssen COVID-19 vaccinated vs unvaccinated matched cohorts.

Table 4. List of example key relevant confounders with an SMD>0.1 after PS matching

Cohort	Covariate name	SMD
BNT162b2 first dose	age group: 30 - 39	-0.13466
mRNA-1273 first dose	age group: 40 - 49	-0.10576
Ad26.COV2-S	age group: 40 - 49	-0.10576
BNT162b2 first dose	age group: 40 - 49	-0.36133
mRNA-1273 first dose	age group: 50 - 59	-0.22304
Ad26.COV2-S	age group: 50 - 59	-0.22304
BNT162b2 first dose	age group: 50 - 59	-0.10526
mRNA-1273 first dose	age group: 60 - 69	0.249811
Ad26.COV2-S	age group: 60 - 69	0.249811
mRNA-1273 first dose	age group: 70 - 79	0.274062
Ad26.COV2-S	age group: 70 - 79	0.274062
BNT162b2 first dose	age group: 70 - 79	0.134135
mRNA-1273 first dose	age group: 80 - 89	0.142449
Ad26.COV2-S	age group: 80 - 89	0.142449

BNT162b2 first dose	age group: 80 - 89	0.40319
BNT162b2 first dose	age group: 90 - 99	0.233354
mRNA-1273 first dose	CHADS2VASc	0.317688
Ad26.COV2-S	CHADS2VASc	0.317688
BNT162b2 first dose	CHADS2VASc	0.524649
mRNA-1273 first dose	Charlson index - Romano adaptation	0.187757
Ad26.COV2-S	Charlson index - Romano adaptation	0.187757
BNT162b2 first dose	Charlson index - Romano adaptation	0.345588

This is not an exhaustive list, but it illustrates the failure of the ‘covariate balance’ diagnostic. Given this, and as pre-specified in our study protocol, we do not report treatment effect estimates for Objectives 1a-2a based on SIDIAP-CMBD ES, as these would be biased due to unresolved observable confounding by indication.

11 Results of Objective 1b and 2b

11.1 Baseline characteristics before and after PS matching

Before propensity score matching, a total of 4.51 million users of Vaxzevria, 10.83 million users of Comirnaty, 248,786 users of Spikevax, and over 980,000 users of Janssen were available for analysis in the different data sources combined.

11.1.1 CPRD AURUM (UK)

CPRD AURUM (UK) contributed 3.8 million people who received 1-dose Vaxzevria, 1.2 million with 2 doses of Vaxzevria, 1.8 million vaccinated with 1-dose Comirnaty, and 1.4 million with two doses of Comirnaty. Baseline characteristics for the 1-dose respective cohorts are detailed in Table 5. These were obtained from our comparative safety interactive Shiny app for the outcome 'all stroke' for illustrative purposes, and would change slightly for other outcomes. Multiple confounders were imbalanced (Std Diff>0.1) before PS matching, including: age, index month, numerous comorbidities (COPD, diabetes, hyperlipidaemia, hypertension, renal impairment, etc), history of relevant cardiovascular disease (atrial fibrillation, cerebrovascular disease, ischaemic heart disease), and medicine/s use (renin-angiotensin system agents, anti-inflammatory medicines, antithrombotic agents, etc). All of these became much more balanced and SMD<0.1 after PS matching. The PS matching process resulted in the comparison of 1.9 million and 1.2 million comparable users of Vaxzevria and Comirnaty respectively.

CPRD AURUM did not identify any other COVID-19 vaccine periods in the study period, and did therefore not contribute to the comparison of Vaxzevria vs Spikevax or to the analysis of Janssen vs either mRNA vaccine.

Table 5. Baseline characteristics of eligible cohorts of vaccinated people identified in CPRD AURUM UK

Characteristic	Before PS matching			After PS matching		
	Vaxzevria	Comirnaty		Vaxzevria	Comirnaty	
	%	%	SMD	%	%	SMD
Age group						
10 - 19	0.4	0.6	-0.03	0.5	0.6	-0.01
20 - 29	4.4	5.4	-0.05	4.8	4.7	0.00
40 - 49	18.3	10.9	0.21	10.5	11.2	-0.03
50 - 59	28.8	16.0	0.31	15.7	17.0	-0.03
60 - 69	21.3	17.8	0.09	23.5	22.2	0.03
70 - 79	14.7	20.4	-0.15	27.1	25.6	0.03
80 - 89	3.6	17.7	-0.47	8.6	9.3	-0.02
100 - 109	0.1	0.1	-0.01	0.1	0.1	0.01
Index month						
1	13.7	47.6	-0.79	37.7	41.4	-0.08
2	29.0	36.3	-0.16	55.0	50.4	0.09
3	45.7	3.6	1.12	4.4	5.2	-0.04
4	9.0	1.6	0.34	2.3	2.4	-0.01
5	2.5	0.4	0.17	0.6	0.6	-0.01
Covid-19 history						
Covid-19 infection prior vaccination	5.5	4.0	0.07	4.6	4.4	0.01
Medical history: General						
Acute respiratory disease	41.4	44.1	-0.05	44.1	43.9	0.00
Attention deficit hyperactivity disorder	0.3	0.2	0.01	0.2	0.2	0.00
Chronic obstructive lung disease	3.1	5.3	-0.11	5.4	5.2	0.01

Crohn's disease	0.5	0.6	-0.01	0.7	0.6	0.00
Dementia	1.2	2.0	-0.07	1.8	1.6	0.01
Depressive disorder	21.3	20.3	0.02	21.3	21.2	0.00
Diabetes mellitus	10.0	15.5	-0.17	15.9	15.6	0.01
Gastroesophageal reflux disease	5.1	5.9	-0.04	5.9	5.9	0.00
Gastrointestinal hemorrhage	8.6	9.7	-0.04	9.7	9.5	0.00
Hyperlipidemia	9.2	13.0	-0.12	13.0	12.8	0.01
Hypertensive disorder	23.8	35.8	-0.26	34.3	33.7	0.01
Lesion of liver	0.9	1.2	-0.03	1.3	1.3	0.00
Obesity	4.7	5.3	-0.03	5.8	5.7	0.00
Osteoarthritis	18.9	28.0	-0.21	26.9	26.5	0.01
Pneumonia	2.8	3.6	-0.05	3.6	3.4	0.01
Psoriasis	4.4	4.7	-0.01	4.9	4.9	0.00
Renal impairment	6.3	13.3	-0.23	11.1	10.9	0.00
Rheumatoid arthritis	1.1	1.6	-0.05	1.6	1.6	0.00
Schizophrenia	0.5	0.4	0.02	0.5	0.5	0.01
Ulcerative colitis	0.7	0.8	-0.01	0.9	0.9	0.00
Urinary tract infectious disease	13.5	16.9	-0.10	16.1	16.0	0.00
Viral hepatitis C	0.2	0.2	0.00	0.2	0.2	0.00
Visual system disorder	39.7	48.7	-0.18	47.2	46.7	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	2.9	6.6	-0.17	5.2	5.1	0.00
Cerebrovascular disease	2.8	5.5	-0.14	3.3	3.2	0.01
Coronary arteriosclerosis	0.8	1.4	-0.06	1.3	1.3	0.00
Heart disease	10.5	19.5	-0.25	17.3	17.1	0.01
Heart failure	1.3	2.6	-0.10	2.2	2.1	0.00
Ischemic heart disease	4.1	8.3	-0.17	7.5	7.3	0.01
Peripheral vascular disease	0.7	1.3	-0.06	1.2	1.2	0.01
Pulmonary embolism	1.0	1.5	-0.05	1.5	1.5	0.00
Venous thrombosis	4.4	6.1	-0.08	5.9	5.7	0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.4	0.7	-0.04	0.7	0.6	0.00
Malignant lymphoma	0.3	0.6	-0.04	0.6	0.6	0.00
Malignant neoplastic disease	8.2	14.7	-0.21	13.4	13.4	0.00
Malignant tumor of breast	1.6	2.7	-0.07	2.7	2.7	0.00
Malignant tumor of colon	0.3	0.7	-0.05	0.6	0.6	0.00
Malignant tumor of lung	0.2	0.3	-0.03	0.3	0.3	0.00
Medication use						
Agents acting on the renin-angiotensin system	9.1	14.0	-0.16	13.5	13.4	0.00
Antibacterials for systemic use	8.6	10.6	-0.07	10.5	10.3	0.01
Antiepileptics	2.5	2.9	-0.03	3.0	3.0	0.00
Antiinflammatory and antirheumatic products	6.5	9.5	-0.11	9.2	9.0	0.00
Antipsoriatics	0.3	0.3	0.00	0.3	0.4	0.00
Antithrombotic agents	4.4	8.9	-0.18	7.5	7.4	0.00
Beta blocking agents	4.5	7.7	-0.13	7.0	7.0	0.00
Calcium channel blockers	6.5	9.9	-0.12	9.7	9.5	0.00
Diuretics	3.4	6.2	-0.13	5.5	5.5	0.00
Drugs for acid related disorders	11.1	15.3	-0.13	14.9	14.8	0.00
Drugs for obstructive airway diseases	9.5	11.9	-0.08	12.2	12.0	0.00
Drugs used in diabetes	4.3	6.8	-0.11	7.1	7.0	0.00
Immunosuppressants	0.4	0.6	-0.03	0.6	0.6	0.00
Lipid modifying agents	9.4	15.7	-0.19	15.3	15.0	0.01
Opioids	5.7	7.3	-0.06	7.3	7.2	0.00
Psycholeptics	2.7	3.1	-0.02	3.2	3.1	0.00

11.1.2 IQVIA France LPD

This data source provided access to 27,709 Vaxzevria and 12,942 Comirnaty 1-dose recipients in the ‘all stroke’ analysis. Matching led to 6,822 and 14,729 in the Vaxzevria and Comirnaty cohorts

respectively. Similar to CPRD AURUM, notable differences existed in many confounders before PS matching, which became balanced (SMD<0.1) after PS matching.

Table 6. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA LPD France

Characteristic	Before PS matching			After PS matching		
	Vaxzevria	Comirnaty		Vaxzevria	Comirnaty	
	%	%	SMD	%	%	SMD
Age group						
20 - 29	0.3	3.7	-0.24	0.9	0.8	0.01
30 - 39	0.6	4.5	-0.25	1.6	1.3	0.02
40 - 49	1.6	8.7	-0.33	3.9	3.1	0.04
50 - 59	23.2	14.1	0.24	17.9	18.9	-0.02
60 - 69	44.1	18.7	0.57	27.4	28.2	-0.02
70 - 79	24.5	28.4	-0.09	33.0	32.8	0.00
80 - 89	4.5	17.9	-0.43	12.8	12.6	0.01
90 - 99	1.1	3.1	-0.14	2.4	2.2	0.01
Gender: female	47.6	56.4	-0.17	54.5	54.2	0.00
Index month						
2	3.6	9.0	-0.22	6.5	5.9	0.02
3	50.3	20.5	0.66	29.9	31.3	-0.03
4	26.5	22.3	0.10	30.6	31.1	-0.01
5	9.7	17.8	-0.24	18.0	17.2	0.02
6	7.0	10.6	-0.13	10.4	9.9	0.02
7	2.6	6.1	-0.17	4.2	4.2	0.00
8	0.1	3.5	-0.25	0.2	0.2	0.01
Covid-19 history						
Covid-19 infection prior vaccination	4.7	6.1	-0.06	5.0	4.8	0.01
Medical history: General						
Acute respiratory disease	44.2	45.5	-0.02	43.8	43.4	0.01
Chronic liver disease	0.5	0.4	0.02	0.5	0.5	-0.01
Chronic obstructive lung disease	4.9	4.4	0.02	4.5	4.7	-0.01
Crohn's disease	0.2	0.4	-0.03	0.3	0.3	-0.01
Dementia	0.3	0.4	-0.02	0.5	0.4	0.01
Depressive disorder	17.9	19.0	-0.03	18.1	18.7	-0.01
Diabetes mellitus	19.9	15.3	0.12	16.7	17.3	-0.01
Gastroesophageal reflux disease	16.3	18.2	-0.05	18.1	18.4	-0.01
Gastrointestinal hemorrhage	3.3	3.8	-0.03	3.5	3.6	0.00
Human immunodeficiency virus infection	0.6	0.4	0.04	0.4	0.4	0.00
Hyperlipidemia	20.8	22.1	-0.03	23.0	23.2	-0.01
Hypertensive disorder	44.1	44.1	0.00	46.9	47.3	-0.01
Lesion of liver	0.6	0.5	0.01	0.6	0.5	0.01
Obesity	1.3	0.9	0.04	1.0	0.9	0.01
Osteoarthritis	22.3	22.7	-0.01	23.5	23.8	-0.01
Pneumonia	4.5	4.8	-0.01	4.6	4.9	-0.01
Psoriasis	4.4	4.2	0.01	4.4	4.5	0.00
Renal impairment	1.4	2.5	-0.08	2.1	2.2	0.00
Rheumatoid arthritis	0.7	1.0	-0.03	0.9	0.9	0.00
Schizophrenia	0.1	0.1	0.01	0.1	<0.1	0.00
Ulcerative colitis	0.3	0.3	-0.01	0.2	0.3	-0.02
Urinary tract infectious disease	7.1	8.9	-0.06	7.9	8.2	-0.01
Viral hepatitis C	0.3	0.2	0.02	0.2	0.3	-0.01
Visual system disorder	21.0	23.7	-0.06	22.6	22.1	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.8	1.5	-0.07	1.1	1.2	0.00
Cerebrovascular disease	4.0	5.2	-0.06	3.0	3.2	-0.01
Coronary arteriosclerosis	2.2	2.3	-0.01	2.5	2.3	0.01
Heart disease	14.7	18.1	-0.09	17.3	16.9	0.01
Heart failure	1.2	2.1	-0.07	1.9	1.7	0.02

Ischemic heart disease	4.9	4.8	0.00	4.8	5.0	-0.01
Peripheral vascular disease	1.6	1.3	0.02	1.5	1.6	0.00
Pulmonary embolism	0.7	1.1	-0.04	0.9	0.9	-0.01
Venous thrombosis	2.0	2.8	-0.05	2.5	2.6	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.3	0.5	-0.03	0.5	0.5	0.00
Malignant lymphoma	0.3	0.6	-0.05	0.5	0.6	-0.01
Malignant neoplasm of anorectum	1.5	0.9	0.06	0.9	1.0	-0.01
Malignant neoplastic disease	7.8	9.2	-0.05	8.6	9.0	-0.01
Malignant tumor of breast	1.8	2.2	-0.03	2.2	2.2	0.00
Malignant tumor of colon	1.5	0.9	0.06	1.0	1.1	0.00
Malignant tumor of urinary bladder	0.2	0.4	-0.03	0.3	0.3	0.00
Primary malignant neoplasm of prostate	1.7	1.7	0.00	1.7	1.7	0.00
Medication use						
Agents acting on the renin-angiotensin system	35.6	33.5	0.04	36.8	37.2	-0.01
Antidepressants	10.3	11.4	-0.03	10.9	11.1	0.00
Antiepileptics	4.0	4.1	-0.01	4.3	4.4	0.00
Antiinflammatory and antirheumatic products	34.5	34.7	0.00	34.7	34.8	0.00
Antineoplastic agents	0.9	0.9	0.00	0.9	1.0	0.00
Antipsoriatics	0.5	0.6	-0.01	0.6	0.6	0.00
Antithrombotic agents	22.8	25.9	-0.07	24.6	24.3	0.01
Beta blocking agents	19.7	21.6	-0.04	22.3	22.4	0.00
Diuretics	19.5	20.4	-0.02	21.7	21.8	0.00
Drugs for acid related disorders	28.0	30.1	-0.04	30.1	30.4	0.00
Drugs for obstructive airway diseases	17.7	17.9	-0.01	18.1	18.2	0.00
Drugs used in diabetes	17.2	12.9	0.12	14.4	14.8	-0.01
Immunosuppressants	0.4	0.7	-0.04	0.6	0.6	0.00
Lipid modifying agents	31.5	29.1	0.05	31.4	31.7	-0.01
Opioids	13.5	12.9	0.02	13.3	13.0	0.01
Psycholeptics	17.3	18.4	-0.03	18.8	18.7	0.00
Psychostimulants, agents used for adhd and nootropics	3.0	3.3	-0.02	3.3	3.3	0.00

The number of people exposed to 1-dose Spikevax was smaller at n=7,644. This number dropped to 7,215 once PS-matched to 2,778 Vaxzevria 1-dose recipients. Similar differences were seen when baseline characteristics were compared, which resolved to SMD<0.1 after PS matching (data not shown, please see interactive web under 'Population characteristics'). No users of the Janssen COVID-19 vaccine were identified in this database.

11.1.3 IQVIA DA Germany

A total of 98,562 Vaxzevria and 391,063 Comirnaty 1-dose users were identified, with 83,366 and 206,343 successfully PS-matched before analysis. Like UK and FR data, we here identified substantial imbalances in the baseline characteristics of recipients of these two vaccines, in terms of age, index month of vaccination, and specific comorbidities. All these were balanced with an SMD<0.1 after PS matching.

Table 7. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA Da Germany

Characteristic	**Before PS matching**			**After PS matching**		
	Vaxzevria	**Comirnaty**		**Vaxzevria**	**Comirnaty**	
	%	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 19	0.5	2.0	-0.14	0.4	0.4	0.01
20 - 29	4.3	7.4	-0.14	3.9	3.6	0.01
30 - 39	5.9	9.9	-0.15	5.6	5.3	0.01
40 - 49	8.7	12.8	-0.14	8.4	8.0	0.02

50 - 59	19.1	22.4	-0.08	19.3	19.0	0.01
60 - 69	37.2	22.5	0.32	37.6	37.3	0.01
70 - 79	18.0	16.1	0.05	18.4	19.6	-0.03
80 - 89	5.4	5.9	-0.02	5.4	5.8	-0.02
90 - 99	1.1	1.0	0.01	1.0	1.1	-0.01
Gender: female	41.2	55.0	-0.28	42.2	42.5	-0.01
Index month						
3	1.9	0.1	0.18	0.5	0.4	0.02
4	22.2	30.7	-0.20	24.4	24.8	-0.01
5	60.4	26.4	0.73	61.3	61.5	0.00
6	13.2	24.5	-0.29	12.1	11.9	0.01
7	2.0	12.7	-0.42	1.6	1.4	0.02
8	0.3	5.5	-0.32	0.1	0.1	0.00
Covid-19 history						
Covid-19 infection prior vaccination	1.2	2.1	-0.07	1.1	1.1	0.00
Medical history: General						
Acute respiratory disease	57.9	59.6	-0.03	58.2	57.8	0.01
Attention deficit hyperactivity disorder	0.6	0.4	0.02	0.6	0.5	0.00
Chronic liver disease	1.0	1.0	0.00	1.0	1.1	-0.01
Chronic obstructive lung disease	11.5	11.3	0.00	11.7	12.1	-0.01
Crohn's disease	0.6	0.8	-0.03	0.6	0.6	0.00
Dementia	2.4	2.2	0.01	2.2	2.4	-0.01
Depressive disorder	22.0	24.2	-0.05	22.6	22.7	0.00
Diabetes mellitus	21.4	20.1	0.03	21.9	22.6	-0.02
Gastroesophageal reflux disease	5.5	5.8	-0.01	5.7	5.8	0.00
Gastrointestinal hemorrhage	3.6	3.2	0.02	3.5	3.5	0.00
Hyperlipidemia	34.5	29.6	0.11	34.8	35.4	-0.01
Hypertensive disorder	49.8	43.8	0.12	51.4	52.2	-0.02
Lesion of liver	1.3	1.4	0.00	1.3	1.4	0.00
Obesity	15.5	15.3	0.01	15.9	16.3	-0.01
Osteoarthritis	33.1	29.0	0.09	33.7	34.2	-0.01
Pneumonia	6.6	6.9	-0.01	6.6	6.7	-0.01
Psoriasis	4.2	3.7	0.02	4.2	4.3	0.00
Renal impairment	8.2	7.3	0.03	8.0	8.4	-0.01
Rheumatoid arthritis	3.7	4.0	-0.01	3.9	4.1	-0.01
Schizophrenia	0.4	0.4	-0.01	0.4	0.4	0.00
Ulcerative colitis	0.8	1.0	-0.02	0.8	0.8	0.00
Urinary tract infectious disease	15.0	17.3	-0.06	15.4	15.5	0.00
Viral hepatitis C	0.4	0.4	0.00	0.4	0.4	0.00
Visual system disorder	26.4	25.4	0.02	26.4	26.8	-0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	3.3	3.3	0.00	3.2	3.4	-0.01
Cerebrovascular disease	7.7	7.3	0.01	6.2	6.5	-0.01
Coronary arteriosclerosis	5.7	5.4	0.01	5.7	6.0	-0.01
Heart disease	31.0	29.4	0.04	31.5	32.5	-0.02
Heart failure	7.3	6.8	0.02	7.3	7.6	-0.01
Ischemic heart disease	13.8	12.7	0.03	14.0	14.4	-0.01
Peripheral vascular disease	6.7	5.8	0.04	6.5	6.8	-0.01
Pulmonary embolism	0.9	1.5	-0.05	0.9	1.0	0.00
Venous thrombosis	5.1	5.7	-0.03	5.2	5.3	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.9	1.2	-0.03	0.9	1.0	-0.01
Malignant lymphoma	0.7	0.9	-0.02	0.7	0.7	-0.01
Malignant neoplasm of anorectum	0.4	0.4	0.00	0.4	0.5	-0.01
Malignant neoplastic disease	12.1	12.8	-0.02	12.4	12.9	-0.01
Malignant tumor of breast	1.7	2.3	-0.04	1.8	1.9	-0.01
Malignant tumor of colon	0.8	0.8	0.00	0.8	0.9	-0.01
Malignant tumor of lung	0.2	0.3	-0.02	0.2	0.3	0.00
Primary malignant neoplasm of prostate	1.6	1.4	0.02	1.7	1.7	0.00
Medication use						

Agents acting on the renin-angiotensin system	35.9	30.6	0.11	37.5	38.3	-0.02
Antibacterials for systemic use	6.4	7.9	-0.06	6.6	6.8	-0.01
Antidepressants	6.1	6.5	-0.02	6.3	6.4	0.00
Antiepileptics	2.4	2.7	-0.02	2.4	2.5	-0.01
Antiinflammatory and antirheumatic products	20.7	19.0	0.04	21.0	21.2	0.00
Antineoplastic agents	0.9	1.0	-0.01	0.9	1.0	0.00
Antipsoriatics	0.3	0.2	0.00	0.3	0.3	0.00
Antithrombotic agents	14.1	14.2	0.00	13.7	14.2	-0.01
Beta blocking agents	23.1	20.8	0.06	24.0	24.7	-0.02
Calcium channel blockers	16.0	13.7	0.06	16.5	16.7	-0.01
Diuretics	19.8	17.2	0.07	20.6	21.0	-0.01
Drugs for acid related disorders	17.4	18.1	-0.02	18.2	18.6	-0.01
Drugs for obstructive airway diseases	9.3	10.2	-0.03	9.8	10.0	-0.01
Drugs used in diabetes	11.4	10.4	0.03	11.7	12.2	-0.01
Immunosuppressants	0.7	1.0	-0.03	0.8	0.8	0.00
Lipid modifying agents	19.5	17.1	0.06	19.5	20.2	-0.02
Opioids	4.9	4.8	0.00	5.0	5.1	-0.01
Psycholeptics	4.3	4.6	-0.02	4.5	4.6	-0.01
Psychostimulants, agents used for adhd and nootropics	0.1	0.1	-0.01	0.1	0.1	0.00

Only 719 people received Spikevax 1-dose vaccination, deeming this data source not useful for the analyses of Vaxzevria vs Spikevax due to limited statistical power.

Finally, DA Germany contained information on 37,723 recipients of the Janssen COVID-19 vaccine. Of these, 18,090 were matched to recipients of 1-dose Comirnaty. Like previously, differences existed between cohorts that were attenuated (and all SMD<0.1) after PS matching (data not shown, please review 'Population characteristics' in our interactive web application).

11.1.4 IPCI NL

A total of 71,084 people vaccinated with 1-dose Vaxzevria and 218,424 with 1-dose Comirnaty were identified for the analysis of 'all stroke' in IPCI. Of these, PS matching led to the inclusion of 21,614 and 48,081 participants respectively (see under the 'Attrition' tab in our interactive web application for more detail).

There were substantial differences between eligible participants, including age, index month, and relevant comorbidities (eg renal impairment) and medicines use (eg antithrombotics). These were attenuated and SMD<0.1 in the matched cohorts (see Table 8).

The number of users of Spikevax was too small (just over 16,000), and therefore underpowered for any comparative safety analysis of this vaccine.

Table 8. Baseline characteristics of eligible cohorts of vaccinated people identified in IPCI

Characteristic	**Before PS matching**			**After PS matching**		
	Vaxzevria	**Comirnaty**		**Vaxzevria**	**Comirnaty**	
	%	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 19	0.2	0.8	-0.08	0.5	0.4	0.01
20 - 29	1.7	5.2	-0.19	4.1	3.6	0.03
30 - 39	1.8	11.3	-0.39	4.6	3.7	0.04
40 - 49	3.0	9.1	-0.26	6.6	5.7	0.04
50 - 59	5.7	21.3	-0.47	13.0	10.7	0.07
60 - 69	83.5	15.0	1.89	59.6	61.5	-0.04
70 - 79	1.7	26.5	-0.76	5.2	7.5	-0.09

80 - 89	1.4	9.9	-0.38	3.9	4.1	-0.01
90 - 99	0.9	1.0	-0.02	2.4	2.7	-0.02
Gender: female	50.3	51.2	-0.02	54.6	55.2	-0.01
Index month						
2	3.0	0.2	0.23	1.1	1.1	0.00
3	18.5	7.6	0.33	7.4	7.5	0.00
4	42.4	24.0	0.40	22.5	24.5	-0.05
5	29.4	30.7	-0.03	52.3	52.3	0.00
6	6.8	37.5	-0.80	16.6	14.5	0.06
Medical history: General						
Attention deficit hyperactivity disorder	1.0	1.5	-0.05	1.4	1.3	0.01
Chronic liver disease	0.2	0.2	0.01	0.2	0.2	0.00
Chronic obstructive lung disease	6.0	5.1	0.04	5.6	6.1	-0.02
Crohn's disease	0.4	0.5	-0.01	0.4	0.4	0.00
Dementia	0.5	1.0	-0.06	1.0	1.2	-0.02
Depressive disorder	11.4	9.3	0.07	11.1	11.2	0.00
Diabetes mellitus	12.5	12.6	0.00	12.4	13.0	-0.02
Gastroesophageal reflux disease	3.4	3.5	-0.01	3.3	3.5	-0.01
Gastrointestinal hemorrhage	6.1	5.8	0.01	5.9	6.1	-0.01
Human immunodeficiency virus infection	0.2	0.1	0.01	0.2	0.2	0.00
Hyperlipidemia	14.8	13.2	0.05	13.1	13.9	-0.02
Hypertensive disorder	32.7	31.3	0.03	30.6	32.6	-0.04
Obesity	8.0	4.9	0.13	7.7	7.7	0.00
Osteoarthritis	18.4	19.7	-0.03	18.3	19.8	-0.04
Pneumonia	11.1	11.4	-0.01	11.3	11.8	-0.02
Psoriasis	4.7	4.3	0.02	4.4	4.6	-0.01
Renal impairment	3.7	6.8	-0.14	5.0	5.6	-0.03
Rheumatoid arthritis	2.7	2.9	-0.01	2.8	3.0	-0.01
Schizophrenia	0.3	0.2	0.02	0.3	0.4	0.00
Urinary tract infectious disease	24.1	26.2	-0.05	26.6	27.2	-0.01
Viral hepatitis C	0.1	0.1	0.02	0.1	0.1	0.01
Visual system disorder	48.5	51.9	-0.07	49.1	50.3	-0.02
Medical history: Cardiovascular disease						
Cerebrovascular disease	4.7	5.7	-0.05	3.3	3.7	-0.03
Coronary arteriosclerosis	0.8	0.8	0.00	0.8	0.8	0.00
Heart disease	17.1	19.6	-0.06	17.5	18.9	-0.04
Heart failure	1.8	2.4	-0.04	2.5	2.8	-0.02
Ischemic heart disease	8.1	9.0	-0.04	8.2	8.8	-0.02
Peripheral vascular disease	1.3	1.4	-0.01	1.4	1.6	-0.01
Venous thrombosis	3.6	3.8	-0.01	3.9	4.3	-0.02
Medical history: Neoplasms						
Hematologic neoplasm	0.2	0.3	-0.01	0.2	0.2	0.00
Malignant lymphoma	0.2	0.3	-0.01	0.2	0.2	-0.01
Malignant neoplastic disease	14.8	17.3	-0.07	15.3	16.1	-0.02
Malignant tumor of breast	2.9	2.8	0.01	2.8	2.9	-0.01
Malignant tumor of urinary bladder	0.5	0.7	-0.03	0.5	0.5	0.00
Medication use						
Agents acting on the renin-angiotensin system	20.9	21.5	-0.01	19.9	21.3	-0.03
Antibacterials for systemic use	12.9	14.5	-0.05	14.6	15.3	-0.02
Antidepressants	9.1	7.9	0.04	8.9	9.3	-0.02
Antiepileptics	2.9	2.6	0.02	3.0	3.1	-0.01
Antineoplastic agents	1.7	2.4	-0.04	2.0	2.1	-0.01
Antipsoriatics	0.5	0.5	0.00	0.5	0.6	-0.01
Antithrombotic agents	13.7	17.5	-0.10	13.7	15.0	-0.04
Beta blocking agents	14.3	17.2	-0.08	14.9	16.1	-0.04
Calcium channel blockers	11.0	11.4	-0.01	10.2	11.1	-0.03
Diuretics	13.3	13.7	-0.01	13.0	14.3	-0.04
Drugs for acid related disorders	25.0	27.3	-0.05	25.6	27.2	-0.04
Drugs for obstructive airway diseases	20.6	20.7	0.00	21.3	21.8	-0.01
Drugs used in diabetes	8.6	8.5	0.00	8.6	9.0	-0.01

Immunosuppressants	1.4	1.9	-0.04	1.7	1.8	-0.01
Lipid modifying agents	22.7	23.6	-0.02	20.8	22.3	-0.04
Opioids	7.0	6.4	0.03	7.3	7.7	-0.01
Psycholeptics	9.9	9.8	0.00	10.6	11.0	-0.01
Psychostimulants, agents used for adhd and nootropics	0.5	0.7	-0.03	0.7	0.7	0.00

A total of 6,206 recipients of the Janssen COVID-19 vaccine were identified. Of them, 4,612 were PS matched to 15,201 users of 1-dose Comirnaty for analysis. These numbers did not provide sufficient power for analysis, with MDRR>5 for all the proposed study outcomes (see 'Power' in our interactive web application).

11.1.5 SIDIAP-CMBD ES

A total of 594,805 people vaccinated with 1-dose Vaxzevria were available. A subset of these were PS matched to users of 1-dose Comirnaty. Although PS matching reduced imbalances in many covariables, strong age-related confounding well beyond the pre-specified threshold of 0.1 SMD remained due to the vaccination guidelines used in Spain and depicted in Figure 7a. For example, age 40-49 had an SMD post-matching of 0.39, age 50-59 of 0.87, age 60-69 of 2.08, age 70-79 of 0.70, and age 80-89 of 0.28. Index month of vaccination also remained strongly imbalanced, with post-matching SMDs of 0.39 for January, 0.28 for February, 0.67 for March, 0.62 for April, 0.32 for May, or 1.01 for June. Due to this remaining confounding and in line with our protocol, the analysis of Vaxzevria vs mRNA vaccines did therefore not continue in SIDIAP.

Conversely, the analysis of Janssen vs Comirnaty was possible in SIDIAP. A total of 138,351 people vaccinated with the Janssen COVID-19 vaccine were identified, and 124,729 of them were PS-matched to 414,973 people who received 1-dose Comirnaty. Despite differences in baseline characteristics, PS matching successfully attenuated these to SMD<0.1 (see Table 9 for a list of pre-specified confounders, and 'Population characteristics' and 'Balance table' in our interactive web application). These numbers provided sufficient power for the analysis of some of the study outcomes (see following sections).

Table 9. Baseline characteristics of eligible cohorts of vaccinated people identified in SIDIAP-CMBD

Characteristic	Before PS matching			After PS matching		
	Janssen	Comirnaty		Janssen	Comirnaty	
	%	%	SMD	%	%	SMD
Age group						
10 - 19	0.3	0.2	0.02	0.3	0.2	0.01
20 - 29	3.0	1.9	0.07	3.0	2.5	0.03
30 - 39	4.8	8.3	-0.14	4.8	5.0	-0.01
40 - 49	40.8	25.6	0.33	42.4	44.7	-0.05
50 - 59	13.7	24.9	-0.29	14.9	14.2	0.02
60 - 69	18.8	2.7	0.54	12.5	10.4	0.07
70 - 79	18.4	19.9	-0.04	21.7	22.7	-0.03
80 - 89	0.2	12.8	-0.53	0.3	0.2	0.02
90 - 99	0.1	3.7	-0.27	0.1	0.1	0.00
Gender: female	46.1	54.1	-0.16	46.3	46.8	-0.01
Index month						
1	0.1	6.6	-0.37	0.1	0.1	-0.01
2	0.1	5.9	-0.35	0.1	0.1	-0.01
4	9.4	18.8	-0.27	11.1	10.8	0.01
5	16.6	22.4	-0.15	19.3	19.6	-0.01
6	73.7	37.7	0.78	69.3	69.2	0.00

Covid-19 history						
Covid-19 infection prior vaccination	8.2	6.6	0.06	7.4	7.7	-0.01
Medical history: General						
Acute respiratory disease	53.8	56.2	-0.05	54.5	54.9	-0.01
Attention deficit hyperactivity disorder	0.3	0.2	0.02	0.3	0.3	0.00
Chronic liver disease	1.8	1.4	0.03	1.7	1.8	0.00
Chronic obstructive lung disease	4.1	5.4	-0.06	4.1	3.9	0.01
Crohn's disease	0.2	0.2	-0.01	0.2	0.2	0.00
Dementia	0.3	2.7	-0.19	0.4	0.4	0.00
Depressive disorder	13.7	15.2	-0.04	13.7	14.0	-0.01
Diabetes mellitus	11.7	14.1	-0.07	11.6	11.5	0.00
Gastroesophageal reflux disease	7.0	7.9	-0.04	7.0	6.9	0.00
Human immunodeficiency virus infection	0.6	0.3	0.05	0.6	0.6	0.00
Hyperlipidemia	21.6	25.9	-0.10	21.7	21.7	0.00
Hypertensive disorder	25.5	34.7	-0.20	25.6	25.0	0.01
Lesion of liver	1.1	1.0	0.01	1.1	1.1	-0.01
Obesity	24.0	25.5	-0.04	24.0	23.9	0.00
Osteoarthritis	16.8	24.5	-0.19	17.0	16.3	0.02
Pneumonia	6.6	8.1	-0.06	6.6	6.7	-0.01
Psoriasis	2.8	3.0	-0.01	2.8	2.9	0.00
Renal impairment	3.8	9.6	-0.24	3.9	3.8	0.00
Rheumatoid arthritis	0.5	0.8	-0.04	0.5	0.6	0.00
Schizophrenia	1.2	0.5	0.07	1.2	1.3	-0.01
Ulcerative colitis	0.4	0.4	-0.01	0.4	0.4	-0.01
Urinary tract infectious disease	19.3	24.0	-0.12	19.4	19.8	-0.01
Viral hepatitis C	1.3	0.9	0.04	1.3	1.3	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	2.1	5.5	-0.18	2.2	2.2	0.00
Cerebrovascular disease	1.8	3.6	-0.12	1.8	2.0	-0.01
Heart disease	12.2	20.1	-0.22	12.4	12.4	0.00
Heart failure	1.5	4.2	-0.16	1.6	1.6	-0.01
Peripheral vascular disease	1.7	2.5	-0.06	1.7	1.7	0.00
Pulmonary embolism	0.4	0.7	-0.04	0.4	0.4	0.00
Venous thrombosis	2.9	3.8	-0.05	2.9	2.8	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.6	1.0	-0.04	0.6	0.7	0.00
Malignant lymphoma	0.2	0.4	-0.04	0.2	0.2	0.00
Malignant neoplasm of anorectum	0.2	0.4	-0.03	0.3	0.3	0.00
Malignant neoplastic disease	7.1	11.9	-0.16	7.5	7.4	0.00
Malignant tumor of breast	1.2	1.8	-0.05	1.3	1.3	0.00
Malignant tumor of colon	0.6	1.2	-0.06	0.7	0.7	0.00
Malignant tumor of lung	0.2	0.2	-0.02	0.2	0.2	0.00
Malignant tumor of urinary bladder	0.5	0.9	-0.05	0.6	0.6	0.00
Primary malignant neoplasm of prostate	0.8	1.6	-0.07	0.9	0.8	0.00
Medication use						
Agents acting on the renin-angiotensin system	18.9	25.7	-0.16	19.0	18.6	0.01
Antibacterials for systemic use	13.6	14.6	-0.03	13.5	13.7	0.00
Antidepressants	13.5	15.8	-0.06	13.6	14.0	-0.01
Antiepileptics	7.2	7.1	0.00	7.2	7.5	-0.01
Antiinflammatory and antirheumatic products	23.9	24.1	0.00	23.9	24.1	0.00
Antineoplastic agents	0.7	1.0	-0.04	0.7	0.8	-0.01
Antipsoriatics	0.9	1.0	-0.02	0.9	0.9	0.00
Antithrombotic agents	9.6	16.3	-0.20	9.7	9.7	0.00
Calcium channel blockers	6.0	9.2	-0.12	6.1	5.9	0.01
Diuretics	12.0	18.9	-0.19	12.2	12.0	0.01
Drugs for obstructive airway diseases	12.6	14.0	-0.04	12.7	12.7	0.00
Drugs used in diabetes	9.0	10.7	-0.06	8.9	8.9	0.00
Immunosuppressants	0.6	1.0	-0.04	0.7	0.9	-0.02
Lipid modifying agents	15.3	19.6	-0.11	15.5	15.4	0.00
Opioids	7.5	8.9	-0.05	7.4	7.5	0.00

Psycholeptics	19.8	23.1	-0.08	19.9	20.2	-0.01
Psychostimulants, agents used for adhd and nootropics	1.1	1.4	-0.03	1.1	1.1	0.00

11.1.6 IQVIA US Hospital CDM

No AZ recipients were identified in the contributing US databases, as this vaccine was not approved by the US FDA at the time of these analyses. A total of 6,199 people were identified who had been vaccinated with 1-dose Janssen COVID-19 vaccine, 281,804 with 1-dose Comirnaty, and 71,018 with 1-dose Spikevax for the analysis of 'all stroke' (see interactive web application for other outcome-specific numbers).

Important differences in key baseline characteristics existed when Janssen and 1-dose Comirnaty recipients were compared before PS matching. These were attenuated and resulted in SMD<0.1 after matching, as demonstrated in Table 10 for the selected list of socio-demographics, index month, comorbidities, and medicine/s use history. As detailed in the next section, this comparison was however not included for analysis, as data-driven identification of covariate imbalance and further review identified relevant confounders that remained with an SMD>0.1, including smoking, alcohol abuse, or systemic corticosteroid use. Also, power was too low and resulted in MDRR>5 for all the study outcomes. Therefore, no analyses were conducted for Hospital CDM.

Table 10. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA US Hospital CDM

Characteristic	Before PS matching			After PS matching		
	Janssen	Comirnaty		Janssen	Comirnaty	
	%	%	SMD	%	%	SMD
Age group						
10 - 19	1.1	1.6	-0.04	0.7	0.5	0.03
20 - 29	8.1	6.5	0.06	4.6	4.0	0.03
30 - 39	13.0	9.2	0.12	9.4	9.2	0.01
40 - 49	14.7	11.5	0.10	11.8	11.0	0.03
50 - 59	25.4	15.9	0.24	26.4	27.9	-0.03
70 - 79	7.9	23.2	-0.43	9.5	10.1	-0.02
80 - 89	2.2	9.0	-0.30	2.4	2.3	0.01
Gender: female	54.3	59.1	-0.10	58.8	59.9	-0.02
Index month						
3	31.1	33.7	-0.06	49.5	50.2	-0.01
4	62.6	20.6	0.94	44.1	43.6	0.01
5	3.1	3.3	-0.02	3.3	3.4	-0.01
6	2.1	1.2	0.07	2.5	2.4	0.01
7	1.1	0.5	0.07	0.7	0.4	0.05
Covid-19 history						
Covid-19 infection prior vaccination	1.9	1.8	0.01	3.4	3.8	-0.02
Medical history: General						
Attention deficit hyperactivity disorder	1.1	1.0	0.01	1.0	1.1	-0.02
Chronic liver disease	2.9	2.3	0.04	5.6	5.2	0.02
Chronic obstructive lung disease	5.0	5.4	-0.02	8.8	8.5	0.01
Crohn's disease	0.5	0.6	-0.01	0.8	0.7	0.01
Depressive disorder	10.9	11.1	-0.01	16.7	16.9	-0.01
Diabetes mellitus	13.9	16.9	-0.08	23.0	23.4	-0.01
Gastroesophageal reflux disease	14.9	18.3	-0.09	24.8	25.6	-0.02
Gastrointestinal hemorrhage	3.6	3.5	0.01	6.0	5.9	0.00
Human immunodeficiency virus infection	1.0	0.8	0.02	1.9	1.6	0.02
Hyperlipidemia	24.8	36.0	-0.25	37.5	39.5	-0.04
Hypertensive disorder	34.0	40.8	-0.14	52.1	54.5	-0.05
Lesion of liver	1.6	1.5	0.01	3.1	2.7	0.02
Obesity	13.2	15.1	-0.06	21.3	22.1	-0.02
Osteoarthritis	15.2	21.3	-0.16	25.7	26.6	-0.02

Pneumonia	3.7	4.0	-0.02	6.1	5.8	0.01
Psoriasis	0.6	1.0	-0.04	1.0	1.1	-0.01
Renal impairment	6.5	8.7	-0.08	12.7	12.6	0.00
Rheumatoid arthritis	1.1	1.7	-0.06	2.2	2.1	0.01
Schizophrenia	0.8	0.3	0.07	1.6	1.4	0.01
Ulcerative colitis	0.3	0.5	-0.03	0.5	0.5	0.01
Urinary tract infectious disease	8.4	9.2	-0.03	12.6	12.0	0.02
Viral hepatitis C	2.3	1.0	0.10	5.0	4.2	0.04
Visual system disorder	9.9	15.0	-0.16	16.6	17.9	-0.03
Medical history: Cardiovascular disease						
Atrial fibrillation	2.6	5.6	-0.15	4.3	4.8	-0.02
Cerebrovascular disease	2.6	4.2	-0.09	3.1	3.4	-0.02
Coronary arteriosclerosis	6.0	10.1	-0.15	10.2	9.8	0.01
Heart disease	14.2	22.5	-0.21	22.0	21.8	0.00
Heart failure	3.5	4.6	-0.06	6.9	6.3	0.03
Ischemic heart disease	4.0	6.0	-0.09	7.3	7.0	0.01
Peripheral vascular disease	2.9	3.6	-0.04	6.4	5.8	0.03
Pulmonary embolism	1.0	1.0	0.00	1.6	1.7	-0.01
Venous thrombosis	1.5	2.0	-0.04	2.6	2.4	0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.9	2.0	-0.09	2.0	2.0	0.00
Malignant lymphoma	0.4	0.9	-0.07	0.5	0.7	-0.03
Malignant neoplasm of anorectum	0.2	0.3	-0.02	0.4	0.3	0.00
Malignant neoplastic disease	6.5	11.6	-0.18	11.4	11.6	-0.01
Malignant tumor of breast	1.6	2.9	-0.09	2.7	2.7	0.00
Malignant tumor of colon	0.3	0.6	-0.04	0.7	0.7	0.00
Malignant tumor of urinary bladder	0.2	0.4	-0.05	0.4	0.3	0.01
Primary malignant neoplasm of prostate	1.1	2.0	-0.07	2.1	2.3	-0.01
Medication use						
Agents acting on the renin-angiotensin system	1.3	1.1	0.02	3.0	2.8	0.01
Antibacterials for systemic use	5.3	4.2	0.05	11.0	10.7	0.01
Antidepressants	1.5	1.0	0.04	3.2	3.2	0.00
Antiepileptics	1.7	1.2	0.05	4.0	3.6	0.03
Antiinflammatory and antirheumatic products	5.1	3.4	0.08	10.6	10.1	0.02
Antineoplastic agents	0.6	1.0	-0.04	1.9	1.6	0.02
Antithrombotic agents	3.9	3.6	0.01	8.0	7.9	0.01
Beta blocking agents	2.0	1.6	0.03	4.6	3.8	0.04
Diuretics	1.4	1.1	0.03	3.1	3.5	-0.02
Drugs for acid related disorders	3.0	2.5	0.03	6.2	5.6	0.02
Drugs for obstructive airway diseases	4.1	3.7	0.02	8.9	8.3	0.02
Drugs used in diabetes	0.2	0.3	-0.01	0.5	0.7	-0.02
Immunosuppressants	0.2	0.3	-0.03	0.5	0.6	0.00
Lipid modifying agents	1.8	1.6	0.02	3.5	3.7	-0.01
Opioids	5.5	5.0	0.02	12.1	11.4	0.02
Psycholeptics	5.7	4.7	0.05	11.8	11.7	0.00
Psychostimulants, agents used for adhd and nootropics	0.1	0.1	0.00	<0.3	0.2	-0.01

11.1.7 IQVIA US Open Claims

As shown during Cohort Diagnostics (see here), US Open Claims contained information on >50 million people vaccinated with 1+ dose of mRNA vaccines, including >30 million recipients of 1-dose Comirnaty and >21 million of 1-dose Spikevax.

A total of 940,232 people vaccinated with Janssen COVID-19 vaccine were identified for the analysis of 'all stroke'. Of these, 621,338 were matched up to 1:4 to 2,387,440 recipients of 1-dose Comirnaty. As shown in Table 11, relevant differences existed in terms of age and index month, which were attenuated after PS matching to an SMD<0.1.

Table 11. Baseline characteristics of eligible cohorts of Janssen and Comirnaty 1-dose vaccinated people identified in IQVIA US Open Claims

Characteristic	Before PS matching			After PS matching		
	Janssen	Comirnaty		Janssen	Comirnaty	
	%	%	SMD	%	%	SMD
Age group						
10 - 19	2.2	4.7	-0.14	1.8	1.8	0.00
20 - 29	13.4	16.0	-0.07	10.5	10.5	0.00
30 - 39	15.2	17.0	-0.05	12.9	12.7	0.00
40 - 49	17.3	16.9	0.01	16.4	16.4	0.00
50 - 59	22.1	17.7	0.11	23.7	24.1	-0.01
60 - 69	18.9	15.1	0.10	21.8	22.0	-0.01
70 - 79	7.6	8.2	-0.02	9.0	8.7	0.01
80 - 89	3.3	4.5	-0.06	3.9	3.8	0.00
Gender: female	47.0	54.5	-0.15	52.0	53.5	-0.03
Index month						
3	23.0	20.0	0.07	26.9	29.8	-0.07
4	33.5	21.6	0.27	35.3	34.7	0.01
5	21.3	11.8	0.26	20.0	17.6	0.06
6	10.5	7.8	0.09	9.1	8.7	0.01
7	5.9	9.0	-0.12	4.7	4.6	0.00
8	5.3	14.1	-0.30	3.7	4.2	-0.02
9	0.5	1.9	-0.13	0.3	0.3	-0.01
Covid-19 history						
Covid-19 infection prior vaccination	2.9	3.3	-0.02	3.4	3.6	-0.01
Medical history: General						
Acute respiratory disease	45.2	45.3	0.00	50.7	52.7	-0.04
Attention deficit hyperactivity disorder	4.4	4.2	0.01	5.1	5.4	-0.02
Chronic liver disease	2.5	2.3	0.01	3.1	3.2	0.00
Chronic obstructive lung disease	5.4	5.0	0.02	6.8	6.5	0.01
Crohn's disease	0.5	0.6	0.00	0.7	0.7	0.00
Dementia	1.2	1.9	-0.06	1.3	1.3	0.00
Depressive disorder	17.1	16.8	0.01	21.1	22.1	-0.03
Diabetes mellitus	12.9	13.0	0.00	16.4	16.6	-0.01
Gastroesophageal reflux disease	15.9	15.8	0.00	20.0	20.5	-0.01
Gastrointestinal hemorrhage	5.9	5.9	0.00	7.1	7.4	-0.01
Human immunodeficiency virus infection	0.4	0.4	-0.01	0.5	0.5	-0.01
Hyperlipidemia	31.4	29.8	0.03	39.0	39.8	-0.02
Hypertensive disorder	30.7	29.3	0.03	38.7	39.2	-0.01
Lesion of liver	1.0	1.0	0.00	1.2	1.3	0.00
Obesity	13.7	13.9	0.00	16.9	17.4	-0.01
Osteoarthritis	25.6	23.4	0.05	31.8	32.2	-0.01
Pneumonia	6.9	7.3	-0.02	8.0	8.1	0.00
Psoriasis	1.9	1.8	0.00	2.4	2.5	0.00
Renal impairment	5.4	6.0	-0.03	6.6	6.6	0.00
Rheumatoid arthritis	1.6	1.7	-0.01	2.1	2.1	0.00
Schizophrenia	0.6	0.7	-0.01	0.7	0.8	0.00
Ulcerative colitis	0.6	0.6	0.00	0.8	0.8	0.00
Urinary tract infectious disease	14.3	16.2	-0.05	17.4	18.2	-0.02
Viral hepatitis C	0.9	0.8	0.02	1.1	1.1	0.00
Visual system disorder	35.9	36.5	-0.01	41.2	42.5	-0.03
Medical history: Cardiovascular disease						
Atrial fibrillation	2.9	3.3	-0.02	3.5	3.4	0.01
Cerebrovascular disease	4.9	5.2	-0.01	5.0	4.9	0.00
Coronary arteriosclerosis	6.1	6.1	0.00	7.6	7.4	0.01
Heart disease	17.9	18.1	0.00	22.0	22.2	-0.01
Heart failure	3.3	3.8	-0.03	4.0	3.9	0.00
Pulmonary embolism	0.8	0.9	-0.01	0.9	1.0	0.00
Venous thrombosis	2.1	2.2	-0.01	2.5	2.6	0.00

Medical history: Neoplasms						
Hematologic neoplasm	1.1	1.2	-0.01	1.4	1.4	0.00
Malignant lymphoma	0.4	0.5	-0.01	0.5	0.5	0.00
Malignant neoplasm of anorectum	0.2	0.2	0.00	0.3	0.3	0.00
Malignant neoplastic disease	8.5	8.7	0.00	10.7	10.6	0.00
Malignant tumor of breast	1.3	1.5	-0.02	1.7	1.7	0.00
Malignant tumor of colon	0.4	0.4	0.00	0.5	0.5	0.00
Malignant tumor of lung	0.2	0.3	-0.01	0.3	0.3	0.00
Malignant tumor of urinary bladder	0.3	0.3	0.00	0.3	0.3	0.00
Primary malignant neoplasm of prostate	1.0	1.0	0.00	1.2	1.2	0.00
Medication use						
Agents acting on the renin-angiotensin system	17.5	15.5	0.05	24.7	23.3	0.03
Antibacterials for systemic use	20.9	21.5	-0.01	26.6	27.6	-0.02
Antidepressants	17.3	16.2	0.03	24.3	25.5	-0.03
Antiepileptics	8.7	7.9	0.03	12.1	12.2	-0.01
Antiinflammatory and antirheumatic products	12.9	12.8	0.00	17.0	17.3	-0.01
Antineoplastic agents	2.3	2.5	-0.01	3.2	3.3	0.00
Antipsoriatics	0.3	0.3	-0.01	0.4	0.4	0.00
Antithrombotic agents	5.0	5.1	0.00	6.3	6.2	0.00
Beta blocking agents	10.4	9.8	0.02	14.4	13.8	0.02
Calcium channel blockers	8.3	7.9	0.02	11.5	11.2	0.01
Diuretics	11.4	10.6	0.03	16.0	16.1	0.00
Drugs for acid related disorders	10.8	10.5	0.01	15.0	15.1	0.00
Drugs for obstructive airway diseases	14.0	13.8	0.01	19.0	19.7	-0.02
Drugs used in diabetes	8.7	8.2	0.02	12.3	12.4	0.00
Immunosuppressants	1.4	1.7	-0.02	2.0	2.1	0.00
Lipid modifying agents	17.6	16.4	0.03	24.6	24.8	0.00
Opioids	7.7	7.1	0.02	10.3	10.3	0.00
Psycholeptics	11.3	10.6	0.02	15.7	16.2	-0.01
Psychostimulants, agents used for adhd and nootropics	3.4	3.2	0.01	4.9	5.3	-0.02

Similarly, 621,497 people vaccinated with Janssen COVID-19 vaccine were matched to 2,289,016 recipients of 1-dose Spikevax. As shown in Table 12, differences in baseline age and index month, as well as in comorbidities like diabetes mellitus or hypertension were identified with an SMD>0.1. These were attenuated and resolved to an SMD<0.1 after PS matching.

Table 12. Baseline characteristics of eligible cohorts of Janssen and Spikevax 1-dose vaccinated people identified in IQVIA US Open Claims

Characteristic	**Before PS matching**			**After PS matching**		
	Janssen	**Spikevax**		**Janssen**	**Spikevax**	
	%	**%**	**SMD**	**%**	**%**	**SMD**
Age group						
10 - 19	2.2	1.6	0.04	1.8	1.9	0.00
20 - 29	13.4	11.5	0.06	10.5	10.7	0.00
30 - 39	15.2	13.1	0.06	12.9	13.4	-0.01
40 - 49	17.3	14.2	0.08	16.4	16.9	-0.01
50 - 59	22.1	17.9	0.10	23.7	22.9	0.02
60 - 69	18.9	20.6	-0.04	21.7	21.4	0.01
70 - 79	7.6	14.0	-0.21	9.0	8.9	0.00
80 - 89	3.3	6.9	-0.16	3.9	4.0	0.00
Gender: female	47.0	54.0	-0.14	52.0	54.1	-0.04
Index month						
3	23.0	29.9	-0.16	26.9	29.5	-0.06
4	33.5	23.9	0.21	35.3	35.4	0.00
5	21.3	11.7	0.26	20.0	18.8	0.03
6	10.5	2.9	0.31	9.1	7.6	0.05
7	5.9	3.8	0.10	4.7	4.8	0.00

8	5.3	2.5	0.15	3.7	3.5	0.01
9	0.5	0.2	0.05	0.3	0.3	0.00
Covid-19 history						
Covid-19 infection prior vaccination	2.9	2.8	0.01	3.4	3.5	0.00
Medical history: General						
Acute respiratory disease	45.2	46.4	-0.02	50.7	50.9	0.00
Attention deficit hyperactivity disorder	4.4	3.5	0.04	5.1	5.0	0.00
Chronic liver disease	2.5	2.9	-0.02	3.1	3.1	0.00
Chronic obstructive lung disease	5.4	7.1	-0.07	6.8	6.7	0.00
Crohn's disease	0.5	0.6	-0.01	0.7	0.7	0.00
Dementia	1.2	1.9	-0.06	1.3	1.3	0.00
Depressive disorder	17.1	18.0	-0.03	21.1	20.9	0.00
Diabetes mellitus	12.9	17.0	-0.12	16.4	16.3	0.00
Gastroesophageal reflux disease	15.9	19.2	-0.09	20.0	19.9	0.00
Gastrointestinal hemorrhage	5.9	7.2	-0.05	7.1	7.2	0.00
Human immunodeficiency virus infection	0.4	0.4	-0.01	0.5	0.5	0.00
Hyperlipidemia	31.4	38.9	-0.16	39.0	38.3	0.01
Hypertensive disorder	30.7	38.1	-0.16	38.7	38.1	0.01
Lesion of liver	1.0	1.2	-0.02	1.2	1.2	0.00
Obesity	13.7	15.4	-0.05	16.9	16.8	0.00
Osteoarthritis	25.6	30.8	-0.12	31.8	31.0	0.02
Pneumonia	6.9	8.0	-0.04	8.0	8.0	0.00
Psoriasis	1.9	2.2	-0.02	2.4	2.4	0.00
Renal impairment	5.4	8.1	-0.11	6.6	6.6	0.00
Rheumatoid arthritis	1.6	2.2	-0.04	2.1	2.2	0.00
Schizophrenia	0.6	0.7	-0.01	0.7	0.7	0.00
Ulcerative colitis	0.6	0.7	-0.02	0.8	0.8	0.00
Urinary tract infectious disease	14.3	17.8	-0.10	17.4	17.9	-0.01
Visual system disorder	35.9	41.3	-0.11	41.2	40.9	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	2.9	4.7	-0.09	3.5	3.5	0.00
Coronary arteriosclerosis	6.1	9.1	-0.11	7.6	7.4	0.00
Heart disease	17.9	23.9	-0.15	22.0	21.8	0.01
Heart failure	3.3	5.0	-0.09	4.0	3.9	0.00
Ischemic heart disease	5.0	7.1	-0.09	6.1	6.0	0.00
Peripheral vascular disease	4.0	6.0	-0.09	4.9	4.9	0.00
Pulmonary embolism	0.8	1.1	-0.04	0.9	1.0	0.00
Venous thrombosis	2.1	2.8	-0.04	2.5	2.5	0.00
Medical history: Neoplasms						
Hematologic neoplasm	1.1	1.5	-0.04	1.4	1.4	0.00
Malignant lymphoma	0.4	0.7	-0.03	0.5	0.5	0.00
Malignant neoplasm of anorectum	0.2	0.3	-0.01	0.3	0.3	0.00
Malignant neoplastic disease	8.5	12.2	-0.12	10.7	10.4	0.01
Malignant tumor of breast	1.3	2.0	-0.06	1.7	1.6	0.00
Malignant tumor of colon	0.4	0.6	-0.03	0.5	0.5	0.00
Malignant tumor of lung	0.2	0.4	-0.03	0.3	0.3	0.00
Malignant tumor of urinary bladder	0.3	0.4	-0.03	0.3	0.3	0.00
Primary malignant neoplasm of prostate	1.0	1.6	-0.06	1.2	1.2	0.00
Medication use						
Agents acting on the renin-angiotensin system	17.5	21.5	-0.10	24.7	22.9	0.04
Antibacterials for systemic use	20.9	23.1	-0.05	26.6	26.5	0.00
Antidepressants	17.3	18.7	-0.04	24.3	24.0	0.01
Antiepileptics	8.7	9.9	-0.04	12.0	11.8	0.01
Antiinflammatory and antirheumatic products	12.8	14.2	-0.04	17.0	17.0	0.00
Antineoplastic agents	2.3	3.0	-0.04	3.2	3.3	0.00
Antipsoriatics	0.3	0.4	-0.01	0.4	0.4	0.00
Antithrombotic agents	5.0	7.1	-0.09	6.3	6.2	0.01
Beta blocking agents	10.4	13.8	-0.10	14.4	13.8	0.02
Calcium channel blockers	8.3	10.8	-0.09	11.5	11.1	0.01
Diuretics	11.4	14.3	-0.09	16.0	15.7	0.01

Drugs for acid related disorders	10.8	13.4	-0.08	15.0	14.9	0.00
Drugs for obstructive airway diseases	14.0	16.1	-0.06	19.0	19.0	0.00
Drugs used in diabetes	8.7	11.0	-0.08	12.3	12.1	0.00
Immunosuppressants	1.4	1.9	-0.04	2.0	2.0	0.00
Lipid modifying agents	17.6	23.5	-0.15	24.6	24.2	0.01
Opioids	7.7	8.3	-0.02	10.3	10.1	0.01
Psycholeptics	11.3	12.3	-0.03	15.7	15.4	0.01
Psychostimulants, agents used for adhd and nootropics	3.4	2.9	0.03	4.9	4.6	0.01

11.2 Diagnostics

As pre-specified per protocol (see Section 9.7.3), three diagnostics were used to identify reliable analyses before fitting outcome models and reporting them. A summary of target-comparator-database diagnostics is provided in Table 13. These results are not outcome-specific, and it is possible that some specific combination of target-comparator-outcome was underpowered (MDRR>5) and therefore excluded later on (see subsequent Sections).

However, both the 'covariate balance' and the 'systematic error' diagnostics are independent of the study outcome, and can therefore be applied at the database-target-comparator level. Failure in the covariate balance was the first checked, and where failed led to a manual review of all the imbalanced covariates by a senior epidemiologist to identify potentially relevant confounders. If such confounders were identified, the analysis was earmarked as biased, and not reported. Conversely, systematic error as identified by >20% of the proposed negative control outcomes being associated with the outcome of interest, was corrected using empirical calibration. This diagnostic did therefore not lead to the exclusion of a database-target-comparator outcome, but rather to the cautious interpretation of results, and to focus on the calibrated estimate/s.

As shown in the table, a number of database-target-comparator analyses failed the covariate balance diagnostic, and were therefore excluded for any further analyses to avoid bias:

- Vaxzevria vs Spikevax and Janssen vs Spikevax in IQVIA DA Germany
- Janssen vs Comirnaty and vs Spikevax in IQVIA US Hospital CDM
- Vaxzevria vs Comirnaty and vs Spikevax in SIDIAP

This exclusion was not only based on the identification of imbalanced covariates, but also after the careful manual review of the covariate balance table by a senior epidemiologist. In all of the cases above, important residual confounding existed, including imbalances in terms of cardiovascular or thromboembolic risk factors that remained associated with exposure despite PS matching:

- Obesity, history of PE, malignancy, ATE, cerebrovascular disease, CKD, and other >50 covariates remained imbalanced with an SMD>0.1 in the analyses of Vaxzevria or Janssen COVID-19 vs Spikevax in IQVIA DA Germany
- Hyperlipidemia, hypertension, and systemic corticosteroid use remained imbalanced with an SMD>0.1 in the Janssen vs mRNA vaccine/s analyses of US Hospital CDM
- Age (with SMD up to >2) and index month (SMD up to >1) in the analysis of Vaxzevria vs any other vaccine in SIDIAP

In addition, some analyses were underpowered, and did not have any outcomes with an MDRR<5. These were therefore not reported at the database-specific level, but were potentially included in the meta-analysis if covariate balance was satisfactory. This group included:

- Vaxzevria vs Comirnaty in IQVIA LPD France
- Vaxzevria vs Spikevax in IQVIA LPD France

All other analyses were reported in subsequent sections of this report, and will be part of future dissemination including scientific manuscripts. As mentioned, some of them did not pass our pre-specified threshold for systematic error, and were therefore highlighted for cautious interpretation, and for exclusive focus on the calibrated estimates:

- Janssen vs Comirnaty in IQVIA DA Germany
- Janssen vs Comirnaty and Janssen vs Spikevax in IQVIA US Open Claims

Table 13. Database-specific target-comparator diagnostics summary

DATABASE	DIAGNOSTIC		*Vaxzevria vs Comirnaty*	*Vaxzevria vs Spikevax*	*Janssen vs Comirnaty*	*Janssen vs Spikevax*
CPRD AURUM						
	Power	*MDRR<5 for 1+ outcomes*	✓	n/a	n/a	n/a
	Covariate balance	*SMD<0.1 for all*	✓	n/a	n/a	n/a
	Systematic error	*<20% associated w exposure*	✓	n/a	n/a	n/a
SIDIAP						
	Power	*MDRR<5 for 1+ outcomes*	x	x	✓	✓
	Covariate balance	*SMD<0.1 for all*	x	x	✓	✓
	Systematic error	*<20% associated w exposure*	x	x	✓	✓
IQVIA DA GERMANY						
	Power	*MDRR<5 for 1+ outcomes*	✓	x	✓	x
	Covariate balance	*SMD<0.1 for all*	✓	x	✓	x
	Systematic error	*<20% associated w exposure*	✓	x	*	x
IQVIA LPD FRANCE						
	Power	*MDRR<5 for 1+ outcomes*	x	x	n/a	n/a
	Covariate balance	*SMD<0.1 for all*	✓	✓	n/a	n/a
	Systematic error	*<20% associated w exposure*	*	*	n/a	n/a
IPCI						
	Power	*MDRR<5 for 1+ outcomes*	✓	n/a	x	
	Covariate balance	*SMD<0.1 for all*	✓	n/a	✓	
	Systematic error	*<20% associated w exposure*	x	n/a	x	
IQVIA US Open Claims						
	Power	*MDRR<5 for 1+ outcomes*	n/a	n/a	✓	✓
	Covariate balance	*SMD<0.1 for all*	n/a	n/a	✓	✓
	Systematic error	*<20% associated w exposure*	n/a	n/a	x	x
IQVIA US HOSPITAL CDM						
	Power	*MDRR<5 for 1+ outcomes*	n/a	n/a	x	x
	Covariate balance	*SMD<0.1 for all*	n/a	n/a	x	x
	Systematic error	*<20% associated w exposure*	n/a	n/a	*	*

Pink = Excluded from further analyses; Orange = Included for meta-analysis, underpowered for database-specific effect estimation; Green = Systematic error detected, only calibrated IRRs should be interpreted

Regarding systematic error in particular, it is worth highlighting the case of IQVIA US Open Claims for the comparison of Janssen vs Comirnaty and Janssen vs Spikevax. In both cases, >20% of the proposed negative control outcomes were associated with the exposure to Janssen. Interestingly, most if not all of

these associations were to the right of the null effect, suggesting that those vaccinated with Janssen had a higher risk of many unrelated/negative control outcomes [see Figure 8]. This was corrected for using empirical calibration, therefore deeming the calibrated estimates more reliable.

Figure 8. Systematic error in the comparison between Janssen and mRNA vaccines in US Open Claims

Figure 8a. Systematic error in the analysis of Janssen vs 1-dose Comirnaty

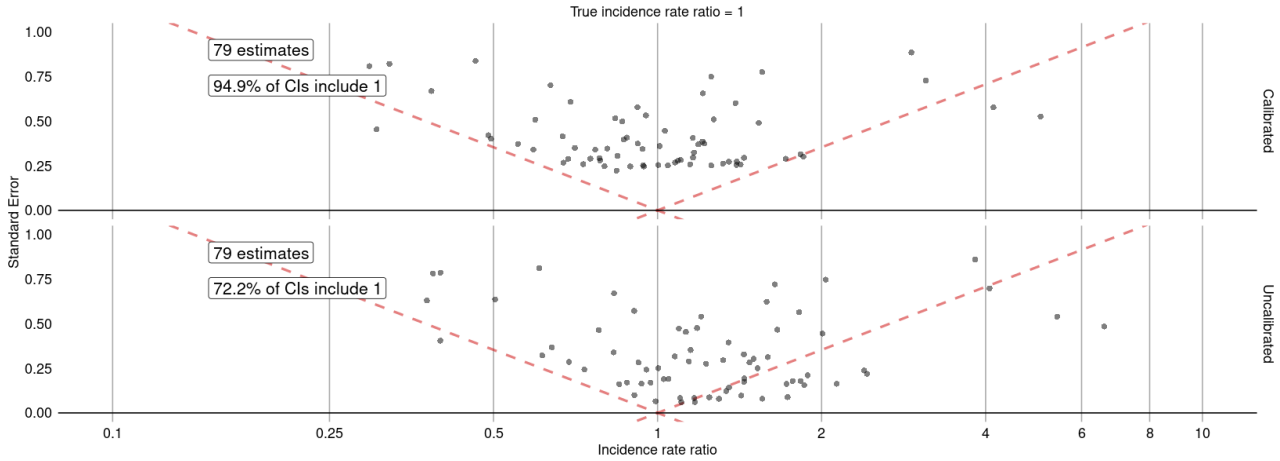
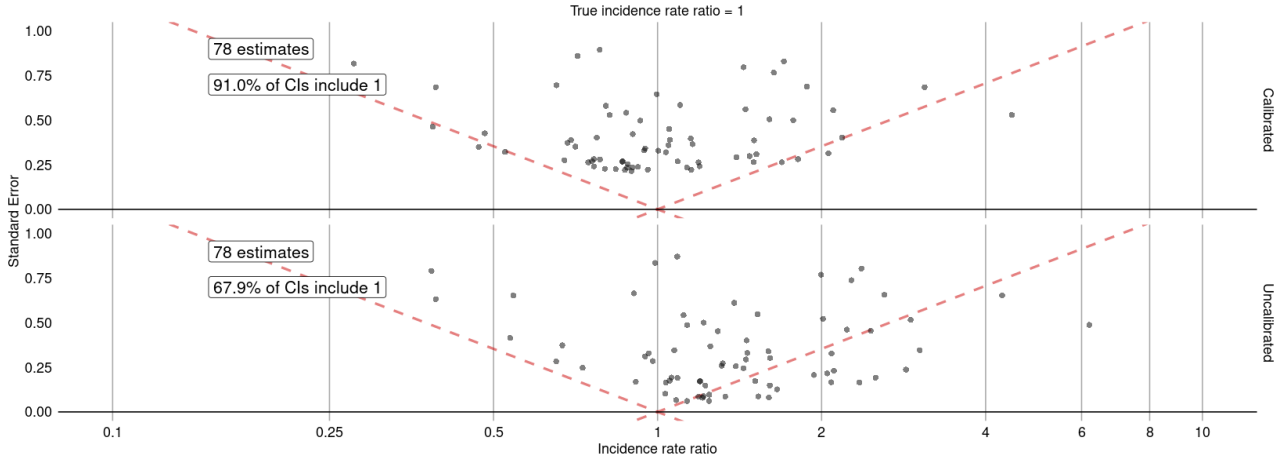


Figure 8b. Systematic error in the analysis of Janssen vs 1-dose Spikevax



11.3 Comparative safety results: Vaxzevria vs mRNA vaccine/s

11.3.1 Database-specific findings

As previously explained, only database-target-comparator-outcome analyses that passed all three diagnostics are reported in this section. CPRD AURUM (UK) and IQVIA DA Germany were the only data sources with reliable results on the comparison between Vaxzevria and mRNA vaccines. More specifically, only the comparison between Vaxzevria and Comirnaty was deemed reliable, and is therefore reported here. All results are reported in detail in Table 14.

Thrombocytopenia was more common following the first dose of Vaxzevria vs Comirnaty in CPRD AURUM, with IR of 6.06/1,000 person-years [5.65-6.48] and 4.89 [4.45-5.37] respectively, and a calibrated IRR of 1.31 [1.16-1.49]. Similar analyses were conducted in IQVIA DA Germany, with similar rates (IR 5.61 [3.91-7.81] in Vaxzevria, 5.03 [3.97-6.27] following Comirnaty) but no difference in risk when both vaccines were compared: calibrated IRR 1.01 [0.63-1.62]. No difference in risk of thrombocytopenia was seen following a second dose of both vaccines in CPRD AURUM: calibrated IRR 0.94 [0.76-1.16], while IQVIA DA Germany had a MDRR >5 for a comparison of second doses.

TTS is reported here as any (VTE/ATE), TTS-VTE or TTS-ATE, with individual outcomes reported in full in Table 14 where diagnostics were satisfactory. The rates of any TTS following a first-dose vaccination in CPRD AURUM were 0.84/1,000 person-years [0.70-1.00] for Vaxzevria, and 0.67 [0.52-0.86] for Comirnaty, equivalent to a calibrated IRR of 1.29 [0.94-1.77]. The calibrated IRR comparing any TTS after a 2nd dose of Vaxzevria vs 2nd dose of Comirnaty in this same data source was 1.16 [0.71-1.89]. While TTS-ATE for 1-dose Vaxzevria vs Comirnaty showed a calibrated IRR of 1.08 [0.23-5.14]), TTS-VTE showed calibrated IRR 2.15 [0.39-11.83].

Regarding VTE, this was a more common event than TTS, with IR of 2.98/1,000 person-years [2.70-3.28] following 1st-dose Vaxzevria, compared to 3.37 [3.00-3.76] following 1st-dose Comirnaty in CPRD AURUM. This equated to a calibrated IRR of 0.91 [0.78-1.06]. Similar analyses of German data (IQVIA DA Germany) showed somewhat similar rates compared to those from the UK: IR 3.91/1,000 person-years [2.53-5.77] and 2.52 [1.80-3.43] following 1-dose Vaxzevria and Comirnaty respectively. The resulting calibrated IRR suggested an increased risk of VTE in this database: 1.61 [0.92-2.83]. The analysis of 2-dose vaccination was only possible in CPRD AURUM, with a resulting calibrated IRR of 0.87 [0.66-1.16].

Looking at specific VTE outcomes, PE was not increased in either CPRD AURUM or IQVIA DA Germany, with calibrated IRR of 0.93 [0.77-1.12] and 0.69 [0.26-1.83] respectively. Similarly, no excess risk was identified in CPRD AURUM following 2-dose vaccination: calibrated IRR 0.86 [0.58-1.26]. Conversely, results for DVT were somewhat different: while no increased risk was seen following 1-dose vaccination with Vaxzevria (vs 1-dose Comirnaty) in CPRD AURUM (calibrated IRR 0.89 [0.71-1.11]), a clear increase in risk was seen in IQVIA DA Germany, with a calibrated IRR of 2.62 [1.34-5.13]. No differential risk was found following 2-dose vaccination in CPRD AURUM (calibrated IRR 0.93 [0.65-1.34]). Particular VTE events of interest including CVST and SVT were rare, with n<5 in each cohort in both CPRD AURUM and IQVIA DA Germany precluding the reporting of IR, with the only exception of SVT in 1-dose Vaxzevria recipients in CPRD AURUM: n=14, IR 0.10/1,000 person-years, calibrated IRR 3.42 [0.92-12.71]. This latter finding should be taken with caution due to low statistical power (MDRR>3.72).

As for ATE, the combined event (MI or ischemic stroke) was sufficiently powered for analysis in both CPRD AURUM and IQVIA DA Germany. The rates of ATE following 1-dose Vaxzevria and 1-dose Comirnaty in the former were IR 2.97/1,000 person-years [2.69-3.27] vs 3.57 [3.19-3.97], equivalent to a calibrated IRR 0.85 [0.73-0.99]. IRs of 3.03 [1.83-4.74] vs 2.83 [2.06-3.80], and

calibrated IRR 0.76 [0.41-1.39] were seen in IQVIA DA Germany for the same comparison. Recipients of 2-dose vaccination were analysed from CPRD AURUM, with a resulting calibrated IRR 1.05 [0.78-1.40].

Specific ATE events were analysed separately, including MI, ischemic stroke, and intestinal infarction. For MI, no differences in risk were noticed following 1-dose vaccination in either CPRD AURUM (calibrated IRR 0.94 [0.78-1.14]) or IQVIA DA Germany (calibrated IRR 0.70 [0.31-1.57]). Similarly neutral results were obtained following 2-dose vaccination in CPRD AURUM: calibrated IRR 0.91 [0.64-1.30]. Somewhat different results were seen for ischemic stroke, with a clear reduction in risk seen amongst Vaxzevria 1-dose users (calibrated IRR 0.66 [0.48-0.92]) but no such difference following 2 doses in CPRD AURUM (calibrated IRR 1.20 [0.66-2.18]), or after 1-dose in IQVIA DA Germany (calibrated IRR 1.34 [0.58-3.09]). Finally, intestinal infarction was too rare for analysis in IQVIA DA Germany (MDRR>5) but deemed well powered in CPRD AURUM: MDRR 2.60 for the 1-dose cohorts and MDRR 1.46 for the 2-dose. The resulting calibrated IRR were 1.09 [0.54-2.19] after 1-dose Vaxzevria (vs 1-dose Comirnaty), and 0.90 [0.66-1.23] following 2 doses.

Table 14. Database-specific findings for the comparison between Vaxzevria and Comirnaty

			N after ps matching	person-years	event	IR per 1,000 py	Calibrated IRR
	Thrombocytopenia						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,195,498	90,381	442	4.89 (4.45-5.37)	
	Target	Vaxzevria 1st dose	1,836,112	136,523	827	6.06 (5.65-6.48)	1.31 (1.16-1.49)
	Comparator	Comirnaty 2nd dose	1,012,563	60,302	347	5.75 (5.16-6.39)	
	Target	Vaxzevria 2nd dose	747,810	38,474	230	5.98 (5.23-6.8)	0.94 (0.76-1.16)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	204,508	15,516	78	5.03 (3.97-6.27)	
	Target	Vaxzevria 1st dose	82,281	6,234	35	5.61 (3.91-7.81)	1.01 (0.63-1.62)
	Any TTS (VTE or ATE)						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,263,613	95,571	64	0.67 (0.52-0.86)	
	Target	Vaxzevria 1st dose	1,934,651	143,950	121	0.84 (0.7-1)	1.29 (0.94-1.77)
	Comparator	Comirnaty 2nd dose	1,076,722	64,277	42	0.65 (0.47-0.88)	
	Target	Vaxzevria 2nd dose	795,629	41,080	38	0.93 (0.65-1.27)	1.16 (0.71-1.89)
	Deep Vein Thrombosis (DVT)						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,247,556	94,341	150	1.59 (1.35-1.87)	
	Target	Vaxzevria 1st dose	1,912,752	142,268	193	1.36 (1.17-1.56)	0.89 (0.71-1.11)
	Comparator	Comirnaty 2nd dose	1,063,064	63,456	96	1.51 (1.23-1.85)	
	Target	Vaxzevria 2nd dose	784,878	40,506	61	1.51 (1.15-1.93)	0.93 (0.65-1.34)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	211,587	16,056	21	1.31 (0.81-2)	
	Target	Vaxzevria 1st dose	85,163	6,454	21	3.25 (2.01-4.97)	2.62 (1.34-5.13)
	Pulmonary embolism (PE)						

CPRD AURUM	Comparator	Comirnaty 1st dose	1,254,781	94,894	197	2.08 (1.8-2.39)	
	Target	Vaxzevria 1st dose	1,922,818	143,038	269	1.88 (1.66-2.12)	0.93 (0.77-1.12)
	Comparator	Comirnaty 2nd dose	1,069,375	63,835	92	1.44 (1.16-1.77)	
	Target	Vaxzevria 2nd dose	789,797	40,767	53	1.3 (0.97-1.7)	0.86 (0.58-1.26)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	212,362	16,115	20	1.24 (0.76-1.92)	
	Target	Vaxzevria 1st dose	85,493	6,479	6	0.93 (0.34-2.02)	0.69 (0.26-1.83)
	Venous thrombo-embolism (VTE)						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,233,788	93,290	314	3.37 (3-3.76)	
	Target	Vaxzevria 1st dose	1,893,469	140,803	420	2.98 (2.7-3.28)	0.91 (0.78-1.06)
	Comparator	Comirnaty 2nd dose	1,050,916	62,715	179	2.85 (2.45-3.3)	
	Target	Vaxzevria 2nd dose	775,486	39,998	105	2.63 (2.15-3.18)	0.87 (0.66-1.16)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	209,244	15,878	40	2.52 (1.8-3.43)	
	Target	Vaxzevria 1st dose	84,436	6,398	25	3.91 (2.53-5.77)	1.61 (0.92-2.83)
	Ischaemic stroke						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,264,894	95,666	76	0.79 (0.63-0.99)	
	Target	Vaxzevria 1st dose	1,936,816	144,104	75	0.52 (0.41-0.65)	0.66 (0.48-0.92)
	Comparator	Comirnaty 2nd dose	1,078,360	64,368	28	0.43 (0.29-0.63)	
	Target	Vaxzevria 2nd dose	796,695	41,129	23	0.56 (0.35-0.84)	1.20 (0.66-2.18)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	210,616	15,982	15	0.94 (0.53-1.55)	
	Target	Vaxzevria 1st dose	84,835	6,429	11	1.71 (0.85-3.06)	1.34 (0.58-3.09)
	Myocardial Infarction (MI)						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,233,874	93,294	201	2.15 (1.87-2.47)	
	Target	Vaxzevria 1st dose	1,895,358	140,942	283	2.01 (1.78-2.26)	0.94 (0.78-1.14)
	Comparator	Comirnaty 2nd dose	1,050,018	62,656	109	1.74 (1.43-2.1)	
	Target	Vaxzevria 2nd dose	774,713	39,952	61	1.53 (1.17-1.96)	0.91 (0.64-1.3)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	208,975	15,856	26	1.64 (1.07-2.4)	
	Target	Vaxzevria 1st dose	84,048	6,368	10	1.57 (0.75-2.89)	0.7 (0.31-1.57)
	Arterial thromboembolism (ATE)						
CPRD AURUM	Comparator	Comirnaty 1st dose	1,227,495	92,807	331	3.57 (3.19-3.97)	
	Target	Vaxzevria 1st dose	1,886,308	140,256	416	2.97 (2.69-3.27)	0.85 (0.73-0.99)
	Comparator	Comirnaty 2nd dose	1,044,491	62,307	153	2.46 (2.08-2.88)	

	Target	Vaxzevria 2nd dose	770,339	39,705	101	2.54 (2.07-3.09)	1.05 (0.78-1.4)
IQVIA DA Germany	Comparator	Comirnaty 1st dose	204,702	15,530	44	2.83 (2.06-3.8)	
	Target	Vaxzevria 1st dose	82,643	6,261	19	3.03 (1.83-4.74)	0.76 (0.41-1.39)

* did not pass the systematic error diagnostics of over 80% uncalibrated CIs cover 1.

11.3.2 Meta-analytic estimates

Meta-analyses were performed, to include results from any database-target-comparator combination that passed covariate balance. Even underpowered database-specific outcomes were included, as these could contribute to the estimation of the overall effect. But database-specific analyses that did not pass covariate balance diagnostics were excluded from the meta-analysis.

Table 15 summarizes the results of the meta-analytic estimates obtained for each of the outcomes of interest. Some outcomes are not reported because they were only available in <2 data sources. Meta-analytic estimates of calibrated IRR are not reported for outcomes where substantial heterogeneity was seen as defined by an I2>40%, in line with our study protocol.

Table 15. Meta-analytic estimates of calibrated IRR for the comparison between 1-dose Vaxzevria and 1-dose Comirnaty

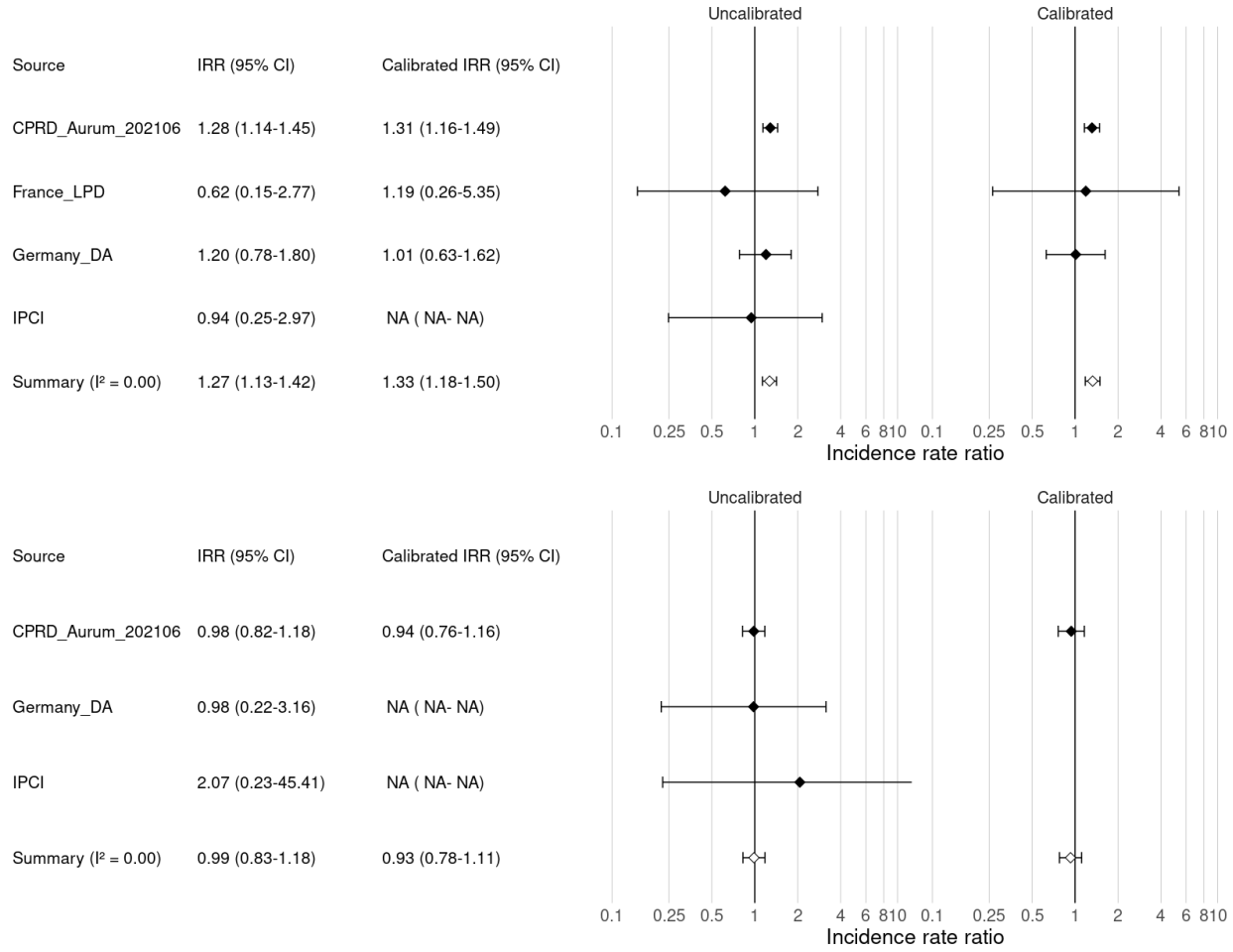
Outcome	N target	n target	N comparator	n comparator	I2	Calibrated IRR [95CI]
Thrombocytopenia	1,954,759	865-872	1,455,437	531-536	0%	1.33 [1.18-1.50]
VTE	2,014,706	451-456	1,498,769	365-370	65%	n/a
PE	2,030,354	270-280	1,516,368	223	0%	0.96 [0.79-1.15]
DVT	2,019,954	214-219	1,508,341	171-176	86%	n/a
CVST	2,032,567	5-10	1,486,737	1-4	0%	4.20 [0.17-106.18]
ATE	2,005,049	440-445	1,486,896	393-398	0%	0.87 [0.75-1.01]
MI	2,015,765	293-303	1,498,059	236-241	0%	0.96 [0.80-1.15]
Ischemic stroke	2,043,695	86-91	1,524,672	91-96	51%	n/a

Forest plots for thrombocytopenia, VTE, ATE and CVST after 1-dose and 2-dose Vaxzevria (vs Comirnaty) are provided in Figures 9 to 12.

All additional outcomes are available for inspection in our interactive web application under 'Forest plot' (please make sure you select the 'Meta analysis' option from the 'Data source' section). No additional associations were identified in the 2-dose analyses.

The meta-analysis of the association between 1-dose Vaxzevria vaccination (compared to Comirnaty) suggested an increased risk of thrombocytopenia following the first dose: meta-analytic calibrated IRR 1.33 [1.18-1.50], see Figure 9. This association was not observed when recipients of 2-dose Vaxzevria vs 2-dose Comirnaty were compared: meta-analytic calibrated IRR 0.93 [0.78-1.11]. See Figure 9.

Figure 9. Forest plot for the association between Vaxzevria (vs Comirnaty) 1-dose [top] and 2-dose vaccination [bottom] and thrombocytopenia



Meta-analytic estimates were not obtained for the association between 1-dose Vaxzevria vs 1-dose Comirnaty and VTE due to heterogeneity across databases (I2 65%). No association was observed in the meta-analysis of 2-dose Vaxzevria vs 2-dose Comirnaty: calibrated IRR 0.84 [0.65-1.09], I2=0%. See Figure 10.

Figure 10. Forest plot for the association between Vaxzevria (vs Comirnaty) 2-dose and VTE

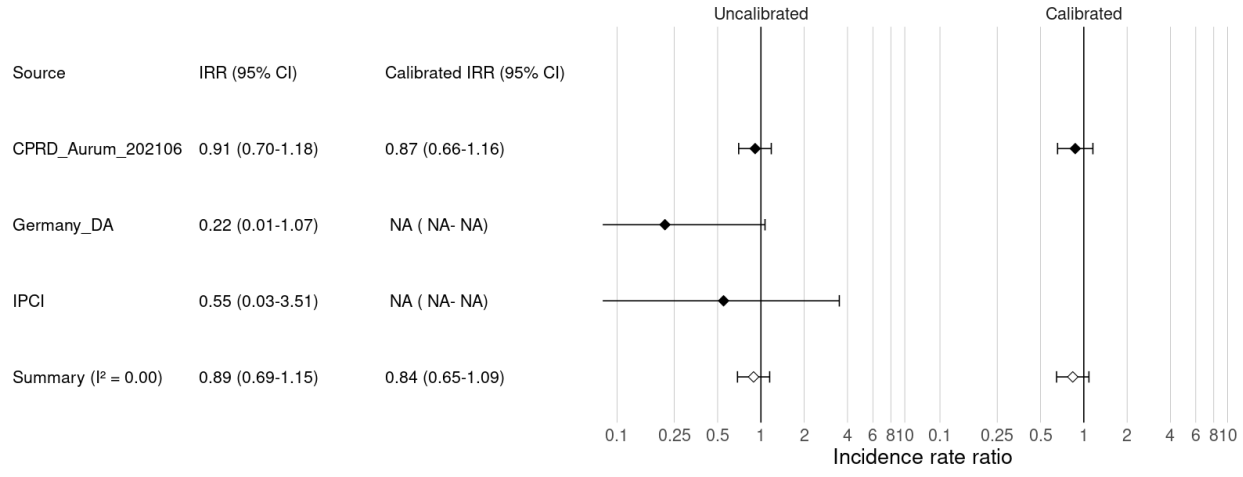
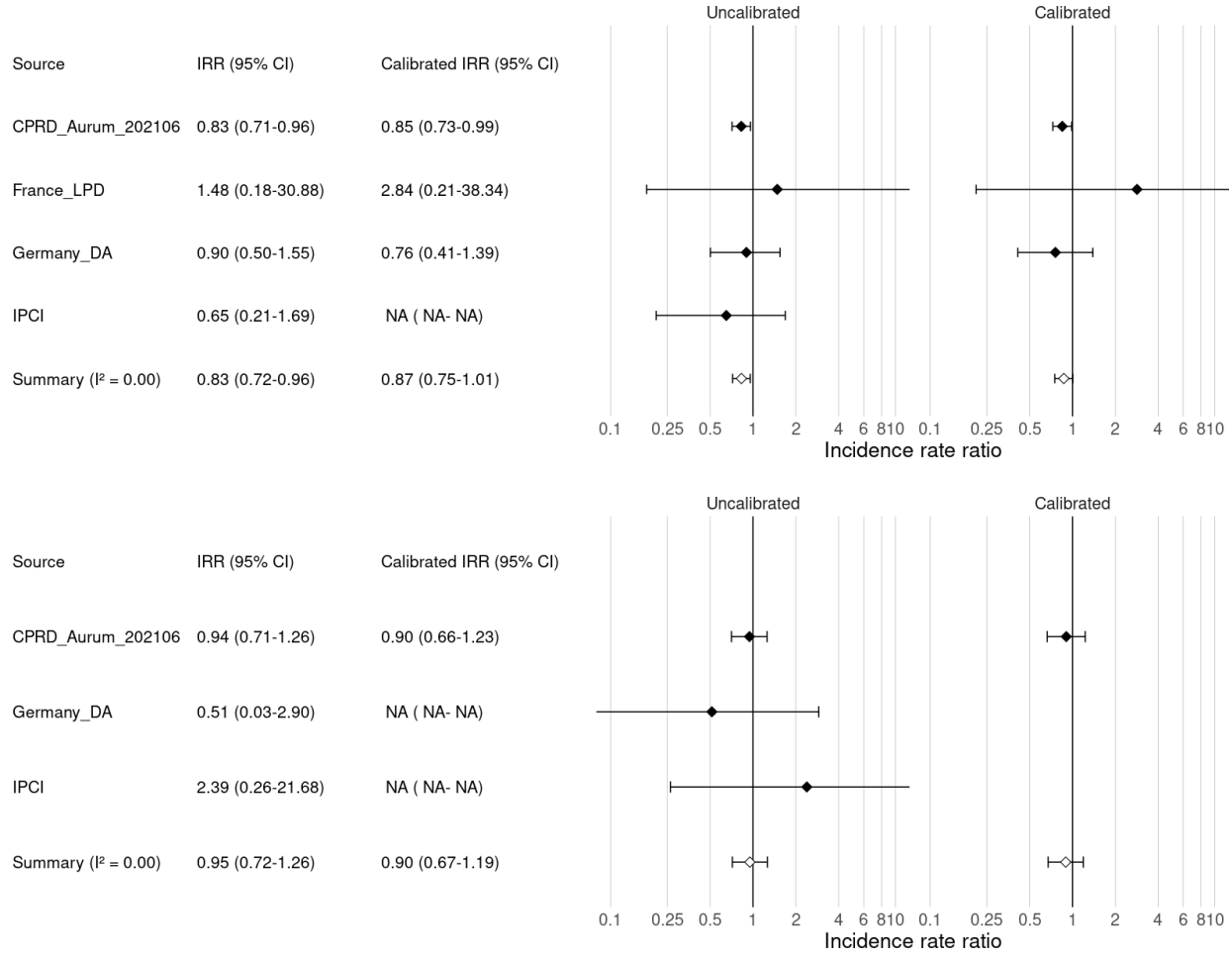


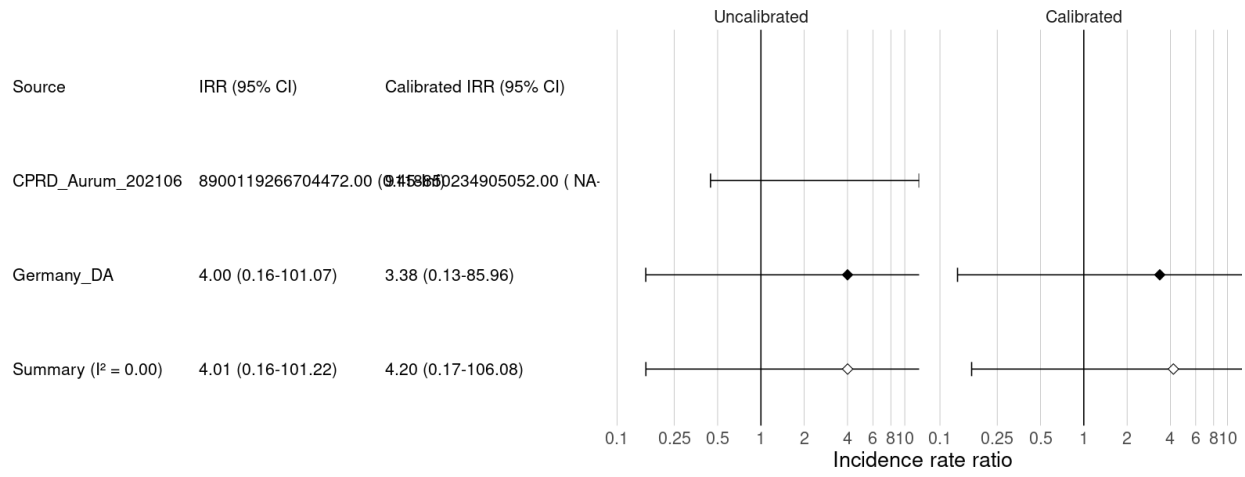
Figure 11 shows the association between 1-dose (top) and 2-dose Vaxzevria vs Comirnaty. The resulting calibrated IRRs were 0.87 [0.75-1.01] and 0.90 [0.67-1.19] respectively.

Figure 11. Forest plot for the association between Vaxzevria (vs Comirnaty) 1-dose [top] and 2-dose vaccination [bottom] and ATE



The meta-analysis of CVST is depicted in Figure 12. Power was limited for this very rare outcome, and did not allow for the analysis of 2-dose vaccination. The meta-analytic calibrated IRR for 1-dose Vaxzevria (vs Comirnaty) was 4.20 [0.17-106.18].

Figure 12. Forest plot for the association between Vaxzevria (vs Comirnaty) 1-dose [top] and 2-dose vaccination [bottom] and ATE



None of the individual events we could meta-analyse (DVT, PE, MI, ischemic stroke) appeared associated with either vaccine, with all calibrated IRR between 0.87 and 0.96 and all confidence intervals including the null (see Table 15).

11.4 Comparative safety results: Janssen vs mRNA vaccine/s

11.4.1 Database-specific findings

All analyses that passed diagnostics are available in detail in Table 16. Database-specific findings were available and passed diagnostics for thrombocytopenia from SIDIAP-CMBD and IQVIA US Open Claims. Rates were similar in both databases when Janssen and 1-dose Comirnaty were compared. Calibrated IRR were 0.77 [0.55-1.08] in SIDIAP-CMBD and 1.03 [0.63-1.70] in IQVIA US Open Claims. Similarly, no difference was seen in thrombocytopenia rates when Janssen and 1-dose Spikevax recipients were compared in IQVIA US Open Claims: calibrated IRR 0.88 [0.56-1.40].

TTS was rare, and no events were identified in the PS-matched participants in SIDIAP-CMBD. In IQVIA US Open Claims, rates of any TTS were similar amongst Janssen vs 1-dose Comirnaty (calibrated IRR 1.11 [0.67-1.84]) and Janssen vs 1-dose Spikevax (calibrated IRR 0.97 [0.61-1.55]). TTS VTE in particular showed a different result, with an apparent increased risk in Janssen vs 1-dose Comirnaty recipients (calibrated IRR 2.45 [0.95-6.29]) and in Janssen vs 1-dose Spikevax (calibrated IRR 1.92 [0.77-4.80]).

As for VTE, results comparing Janssen to 1-dose Comirnaty were available from SIDIAP-CMBD and IQVIA US Open Claims. Both showed a similar risk for recipients of both vaccines, with calibrated IRR 1.03 [0.55-1.93] and 1.06 [0.64-1.74] respectively. Similar findings were seen for the comparison of Janssen vs 1-dose Spikevax: calibrated IRR 0.99 [0.62-1.56].

Individual VTE events were also studied in the same data sources. The calibrated IRRs for DVT when Janssen and 1-dose Comirnaty were compared were 0.94 [0.45-1.96] in SIDIAP-CMBD and 0.98 [0.59-1.63] in IQVIA US Open Claims. Similar findings were obtained for the comparison of Janssen vs 1-dose Spikevax in the latter: calibrated IRR 0.92 [0.57-1.48]. As for PE, the results were similar, with no differential risk in Janssen vs 1-dose Comirnaty recipients: calibrated IRR 1.06 [0.37-3.07] in SIDIAP-CMBD, and 1.18 [0.70-1.98] in IQVIA US Open Claims. Equivalent analyses for Janssen vs 1-dose Spikevax resulted in a calibrated IRR of 1.15 [0.71-1.87]. SVT was only analysed with sufficient power (MDRR<5) in IQVIA US Open Claims, with calibrated IRR 1.46 [0.59-3.61] for the comparison of Janssen vs 1-dose Comirnaty, and 1.48 [0.60-3.65] for Janssen vs 1-dose Spikevax. CVST was too rare, with <5 cases per cohort and MDRR>5 in all the contributing data sources.

For the composite ATE, the analyses were well powered in both SIDIAP CMBD and IQVIA US Open Claims. In the comparison between Janssen and 1-dose Comirnaty in SIDIAP CMBD rates were 6.27/1,000 person-years [4.34-8.76] vs 5.55 [4.60-6.65] respectively, equivalent to a calibrated IRR 0.93 [0.62-1.39]. Rates were somewhat higher in IQVIA US Open Claims, with rates ranging between 13.3 and 15.8/1,000 person-years, and calibrated IRR 0.92 [0.57-1.48] for Janssen vs 1-dose Comirnaty, and 0.83 [0.54-1.28] for Janssen vs 1-dose Spikevax.

Regarding individual ATE events, ischemic stroke was analysed with sufficient power in both SIDIAP CMBD and IQVIA US Open Claims. The resulting calibrated IRRs for the comparison between Janssen and 1-dose Comirnaty were similar in both data sources: 1.04 [0.59-1.81] and 1.02 [0.62-1.67] respectively. The same analysis for Janssen vs 1-dose Spikevax showed a similar treatment effect, with calibrated IRR 0.93 [0.59-1.47]. Similar findings were seen for MI, with similar risk amongst Janssen and 1-dose Comirnaty recipients in SIDIAP CMBD (calibrated IRR 0.81 [0.38-1.71]) and 1.02 [0.62-1.68] in IQVIA US Open Claims. The equivalent calibrated IRR for the comparison between Janssen and 1-dose Spikevax was 0.86 [0.54-1.36]. Finally, intestinal infarction was only powered for analysis in IQVIA US Open Claims. Risk of this particular event appeared lower amongst Janssen vaccine recipients, with calibrated IRR for Janssen vs 1-dose Comirnaty was 0.35 [0.14-0.87], and for Janssen vs 1-dose Spikevax 0.29 [0.12-0.71].

Table 16. Database-specific findings for the comparison between Janssen COVID-19 and Comirnaty

			N after ps matching	person-years	event	IR per 1,000 py	Calibrated IRR
	Thrombocytopenia						
SIDIAP CMBDES	Comparator	Comirnaty 1st dose	386,334	19,944	197	9.88 (8.55-11.36)	
	Target	Janssen 1st dose	106,217	5,037	49	9.73 (7.2-12.86)	0.77 (0.55-1.08)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,364,195	172,698	470	2.72 (2.48-2.98)	
	Target	Janssen 1st dose	628,293	46,997	170	3.62 (3.09-4.2)	1.03 (0.63-1.7)
	Comparator	Spikevax 1st dose	2,231,498	169,780	484	2.85 (2.6-3.12)	
	Target	Janssen 1st dose	628,459	47,007	170	3.62 (3.09-4.2)	0.88 (0.56-1.4)
	TTS DVT						
IQVIA US Open Claims	Comparator	Spikevax 1st dose	2,271,774	172,851	12	0.07 (0.04-0.12)	
	Target	Janssen 1st dose	639,496	47,843	6	0.13 (0.05-0.27)	1.35 (0.45-4.05)
	TTS VTE						
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,404,904	175,752	13	0.07 (0.04-0.13)	
	Target	Janssen 1st dose	639,269	47,828	11	0.23 (0.11-0.41)	2.45 (0.95-6.29)
	Comparator	Spikevax 1st dose	2,271,552	172,835	14	0.08 (0.04-0.14)	
	Target	Janssen 1st dose	639,432	47,838	11	0.23 (0.11-0.41)	1.92 (0.77-4.8)
	Any TTS (VTE or ATE)						
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,365,254	172,778	378	2.19 (1.97-2.42)	
	Target	Janssen 1st dose	628,571	47,019	146	3.11 (2.62-3.65)	1.11 (0.67-1.84)
	Comparator	Spikevax 1st dose	2,232,550	169,861	380	2.24 (2.02-2.47)	
	Target	Janssen 1st dose	628,737	47,028	146	3.1 (2.62-3.65)	0.97 (0.61-1.55)
	Deep Vein Thrombosis (DVT)						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	421,532	22,028	33	1.50 (1.03-2.10)	
	Target	Janssen 1st dose	116,087	5,582	10	1.79 (0.86-3.29)	0.94 (0.45-1.96)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,363,428	172,627	347	2.01 (1.8-2.23)	
	Target	Janssen 1st dose	628,002	46,974	121	2.58 (2.14-3.08)	0.98 (0.59-1.63)
	Comparator	Spikevax 1st dose	2,230,157	169,676	336	1.98 (1.77-2.2)	
	Target	Janssen 1st dose	628,164	46,983	121	2.58 (2.14-3.08)	0.92 (0.57-1.48)

	Pulmonary embolism (PE)						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	422,330	22,072	14	0.63 (0.35-1.06)	
	Target	Janssen 1st dose	116,315	5,593	5	0.89 (0.29-2.09)	1.06 (0.37-3.07)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,380,869	173,941	250	1.44 (1.26-1.63)	
	Target	Janssen 1st dose	632,834	47,339	105	2.22 (1.81-2.69)	1.18 (0.7-1.98)
	Comparator	Spikevax 1st dose	2,247,746	171,017	227	1.33 (1.16-1.51)	
	Target	Janssen 1st dose	632,997	47,349	105	2.22 (1.81-2.68)	1.15 (0.71-1.87)
	Splanchnic/Visceral Thrombosis (SVT)						
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,404,366	175,711	19	0.11 (0.07-0.17)	
	Target	Janssen 1st dose	639,111	47,816	10	0.21 (0.1-0.38)	1.46 (0.59-3.61)
	Comparator	Spikevax 1st dose	2,271,071	172,798	17	0.1 (0.06-0.16)	
	Target	Janssen 1st dose	639,274	47,826	10	0.21 (0.1-0.38)	1.48 (0.60-3.65)
	Venous thrombo-embolism (VTE)						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	420,502	21,960	42	1.91 (1.38-2.59)	
	Target	Janssen 1st dose	115,760	,5,562	14	2.52 (1.38-4.22)	1.03 (0.55-1.93)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,348,419	171,499	506	2.95 (2.7-3.22)	
	Target	Janssen 1st dose	624,001	46,670	190	4.07 (3.51-4.69)	1.06 (0.64-1.74)
	Comparator	Spikevax 1st dose	2,215,499	168,558	488	2.9 (2.64-3.16)	
	Target	Janssen 1st dose	624,163	46,679	190	4.07 (3.51-4.69)	0.99 (0.62-1.56)
	Ischaemic stroke						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	417,793	21,749	61	2.80 (2.15-3.60)	
	Target	Janssen 1st dose	114,999	5,509	18	3.27 (1.94-5.16)	1.04 (0.59-1.81)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,348,140	171,471	540	3.15 (2.89-3.43)	
	Target	Janssen 1st dose	623,396	46,622	193	4.14 (3.58-4.77)	1.02 (0.62-1.67)
	Comparator	Spikevax 1st dose	2,214,613	168,485	533	3.16 (2.9-3.44)	
	Target	Janssen 1st dose	623,557	46,632	193	4.14 (3.58-4.77)	0.93 (0.59-1.47)
	Myocardial Infarction (MI)						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	418,734	21,822	38	1.74 (1.23-2.39)	
	Target	Janssen 1st dose	115,276	5,528	10	1.81 (0.87-3.33)	0.81 (0.38-1.71)

IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,356,142	172,074	472	2.74 (2.5-3)	
	Target	Janssen 1st dose	625,168	46,757	168	3.59 (3.07-4.18)	1.02 (0.62-1.68)
	Comparator	Spikevax 1st dose	2,222,711	169,104	513	3.03 (2.78-3.31)	
	Target	Janssen 1st dose	625,329	46,766	168	3.59 (3.07-4.18)	0.86 (0.54-1.36)
	Intestinal infarction						
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,401,293	175,480	53	0.30 (0.23-0.40)	
	Target	Janssen 1st dose	638,257	47,752	7	0.15 (0.06-0.3)	0.35 (0.14-0.87)
	Comparator	Spikevax 1st dose	2,267,972	172,560	54	0.31 (0.24-0.41)	
	Target	Janssen 1st dose	638,418	47,761	7	0.15 (0.06-0.3)	0.29 (0.12-0.73)
	Arterial thromboembolism (ATE)						
SIDIAP-CMBD ES	Comparator	Comirnaty 1st dose	413,039	21,426	119	5.55 (4.6-6.65)	
	Target	Janssen 1st dose	113,588	5,421	34	6.27 (4.34-8.76)	0.93 (0.62-1.39)
IQVIA US Open Claims	Comparator	Comirnaty 1st dose	2,304,844	168,208	2,231	13.26 (12.72-13.83)	
	Target	Janssen 1st dose	610,895	45,673	720	15.76 (14.63-16.96)	0.92 (0.57-1.48)
	Comparator	Spikevax 1st dose	2,171,445	165,188	2,246	13.6 (13.04-14.17)	
	Target	Janssen 1st dose	611,054	45,682	720	15.76 (14.63-16.96)	0.83 (0.54-1.28)

11.4.2 Meta-analytic estimates

A summary of the findings of the meta-analysis of comparative safety analyses of Janssen vs mRNA vaccines is reported in Table 17. Only target-comparator-outcomes with >1 database-specific estimate available are reported. Those with I2>0.40 are listed in the table, but with no meta-analytic IRR reported (shown as 'N/A' in Table 17).

To facilitate interpretation, it is important to remind the reader that IQVIA US Open Claims, the largest contributor to these analyses, showed clear evidence of systematic error with "positive bias", where most of the negative control outcomes associated with exposure had an uncalibrated IRR>1. As a result, uncalibrated IRR from this data source should be disregarded, and calibrated ones preferred. The same would apply to the meta-analytic estimates reported here.

Table 17. Meta-analytic estimates of calibrated IRR for the comparison between Janssen COVID-19 and 1-dose mRNA vaccines

Outcome	**N target**	**n target***	**N comparator**	**n comparator ***	**I2**	**Calibrated IRR [95CI]**
Janssen vs 1-dose Comirnaty						
Thrombocytopenia	752,443	231	2,815,746	681	78%	N/A

TTS DVT	756,112	6-11	2,828,928	10-15	0%	1.83 (0.62-5.38)
TTS VTE	756,029	11-16	2,828,614	13-18	0%	2.26 (0.93-5.52)
TTS ATE	755,875	5-10	2,828,146	16-21	0%	0.62 (0.2-1.98)
VTE	758,035	212	2,835,352	554	73%	N/A
PE	767,674	110-120	2,870,522	264-274	6%	1.17 (0.7-1.97)
DVT	762,517	131-141	2,851,976	380-390	14%	0.99 (0.58-1.67)
SVT	755,858	10-15	2,828,030	19-24	0%	1.52 (0.67-3.47)
CVST	658,162	5-10	2,473,677	6-11	0%	2.23 (0.61-8.18)
ATE	746,964	754-769	2,797,654	2,363-2,373	0%	0.89 (0.58-1.37)
MI	763,235	178-193	2,832,707	517-527	0%	0.97 (0.61-1.53)
Ischemic stroke	756,774	211-221	2,838,983	601-611	0%	0.99 (0.63-1.55)
Intestinal infarction	754,966	12-17	2,824,851	53-58	0%	0.37 (0.15-0.89)

* Due to information governance rules, database-specific counts of <5 were not available. Therefore, summary (meta-analytic) n of events are an approximation to +/- 5 or 10 in some instances

The meta-analysis of the association between Janssen vs mRNA vaccines and VTE included 3 databases (IQVIA Germany DA, SIDIAP CMBD ES, and US Open Claims) for the comparison vs 1-dose Comirnaty. However, I2 was 73%, and therefore no meta-analytic estimate is provided in Table 17. The comparison vs 1-dose Spikevax was only conducted within the US Open Claims data, therefore no meta-analysis was done.

The analysis of individual VTE outcomes showed a similar picture for the most common events, PE (calibrated IRR 1.17 [0.70-1.97] for Janssen vs Comirnaty, Figure 13) and DVT (calibrated IRR 0.99 [0.58-1.67] for Janssen vs Comirnaty, Figure 14). Meta-analytic estimates for rare VTE events SVT and CVST were only available for the comparison vs 1-dose Comirnaty due to limited power. Calibrated IRR for SVT was 1.52 [0.67-3.47], and 2.23 [0.61-8.18] for CVST. Both were the product of two database-specific estimates that, despite uncertainty, both pointed in the same direction and suggested an association would be towards an increased risk (see Figure 15 and Figure 16).

Figure 13.- Forest plot for the association between Janssen vs 1-dose Comirnaty and PE

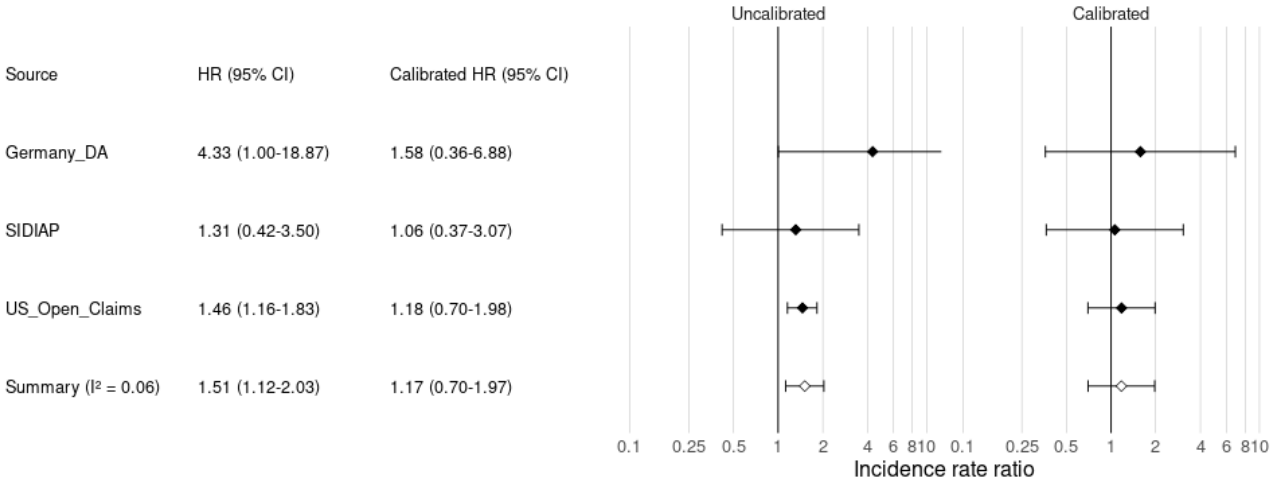


Figure 14. Forest plot for the association between Janssen vs 1-dose Comirnaty and DVT

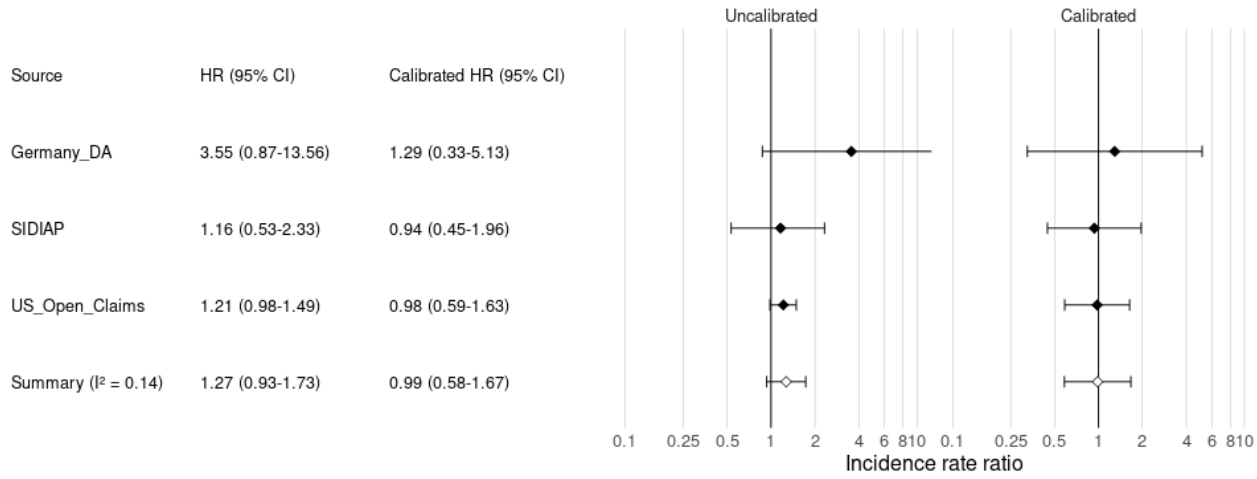


Figure 15.- Forest plot for the association between Janssen vs 1-dose Comirnaty and SVT

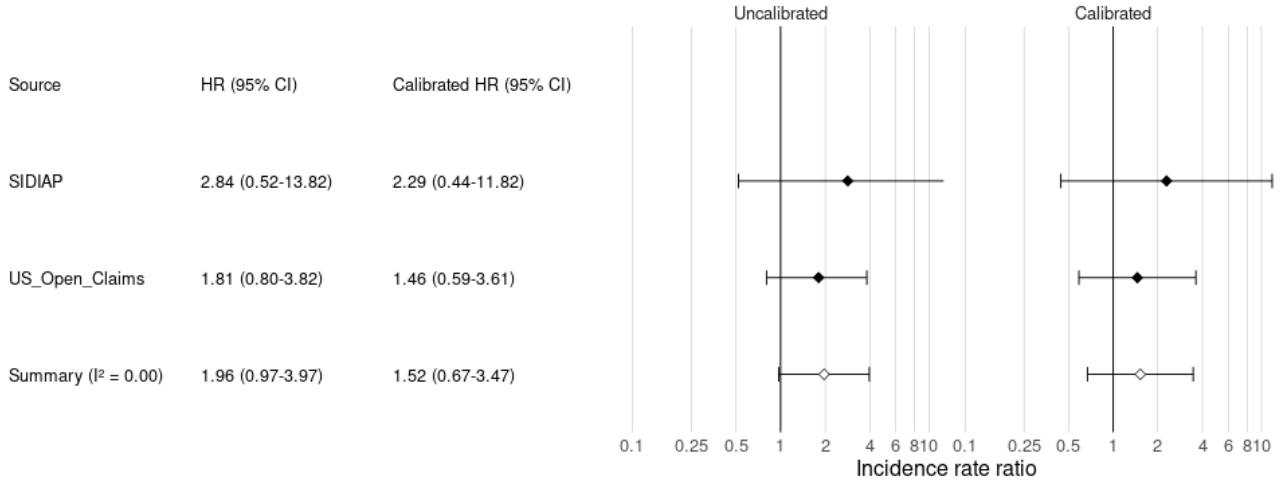
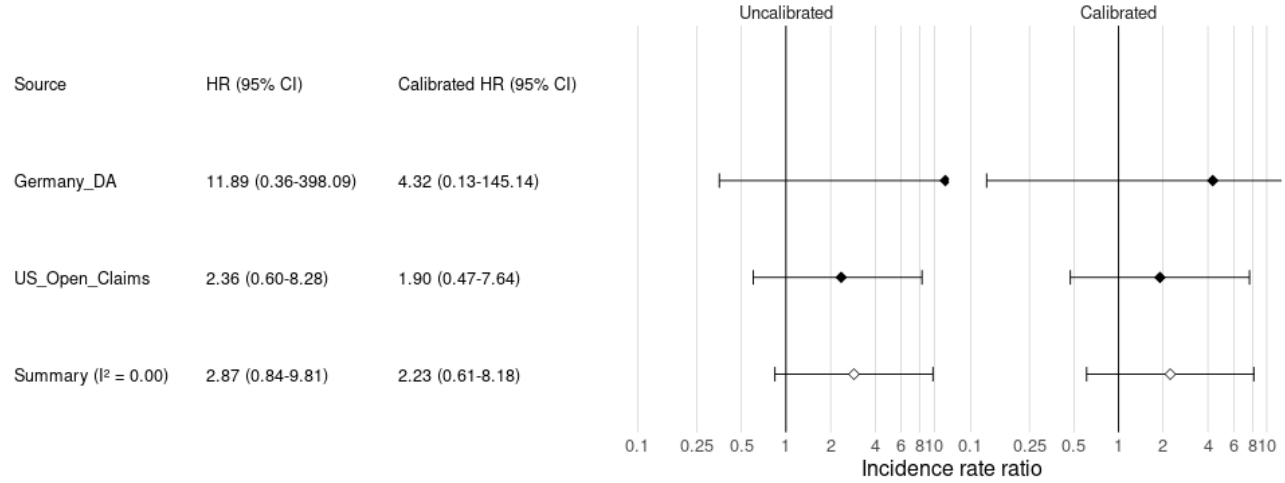
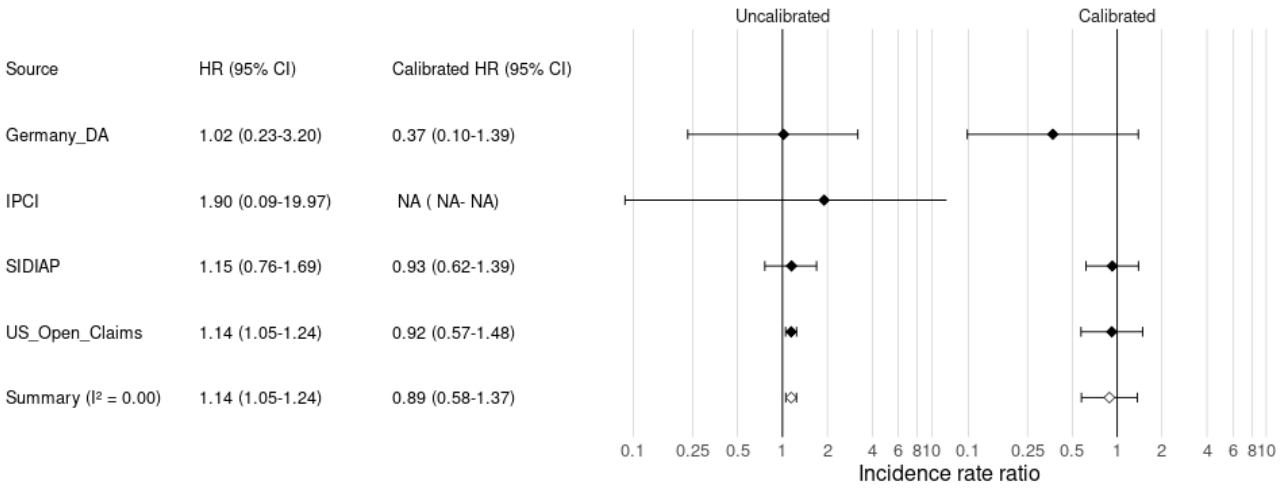


Figure 16. Forest plot for the association between Janssen vs 1-dose Comirnaty and CVST



As for ATE, the meta-analysis was better powered for Janssen vs 1-dose Comirnaty, pooling database-specific findings from 4 data sources (IQVIA DA Germany, IPCI NL, SIDIAP CMBD ES, IQVIA US Open Claims). The resulting meta-analytic calibrated IRR was 0.89 [0.58-1.37]. Figure 17 summarizes and depicts Forest plots for these findings.

Figure 17. Forest plot for the association between Janssen vs 1-dose Comirnaty and ATE



The meta-analysis of MI also included the same databases mentioned above for ATE. The combination of 4 database-specific estimates for Janssen vs 1-dose Comirnaty showed a pooled calibrated IRR of 0.97 [0.61-1.53]. See Figure 18.

Figure 18. Forest plot for the association between Janssen vs 1-dose Comirnaty and MI

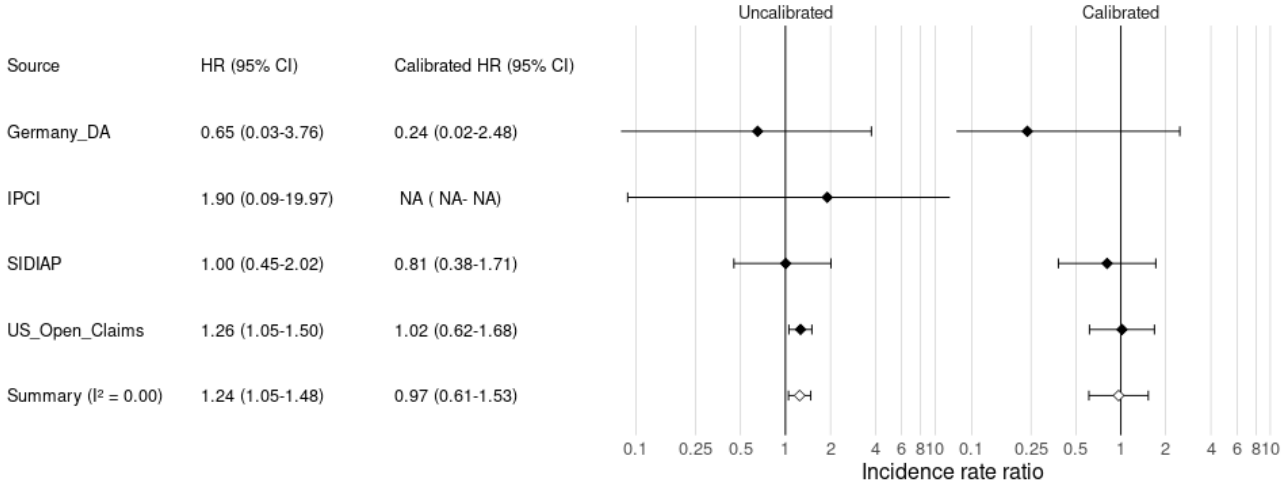
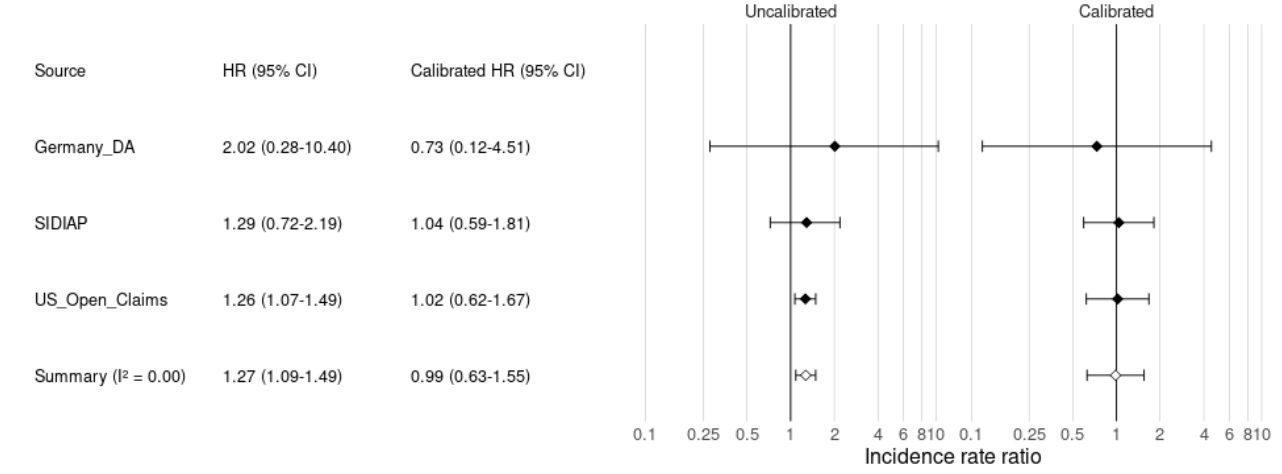


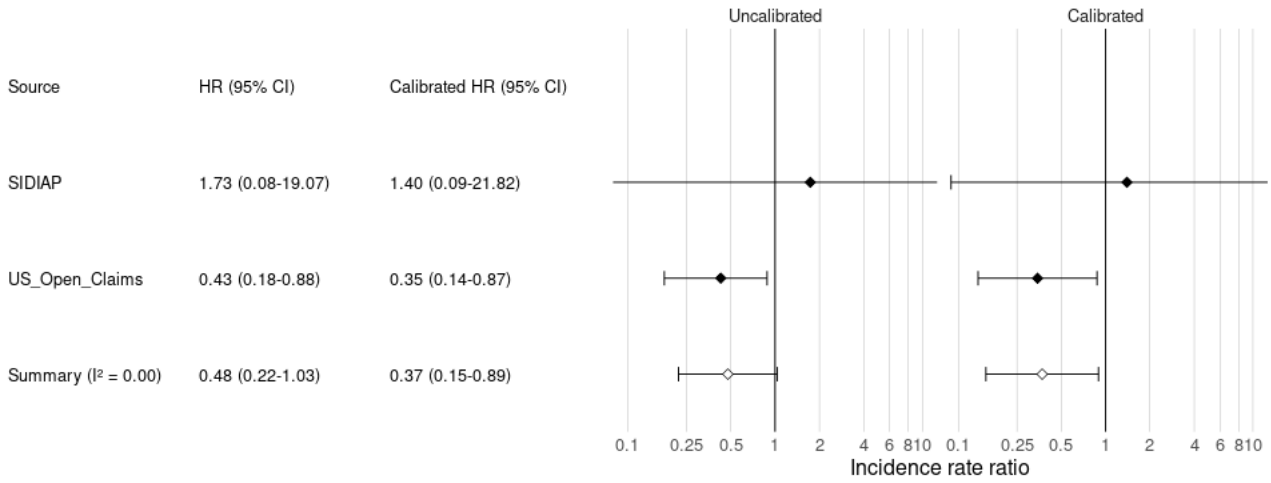
Figure 19 depicts meta-analytic estimates for association between vaccination with Janssen and ischemic stroke, with calibrated IRR of 0.99 [0.63-1.55].

Figure 19. Forest plot for the association between Janssen vs 1-dose Comirnaty and ischemic stroke



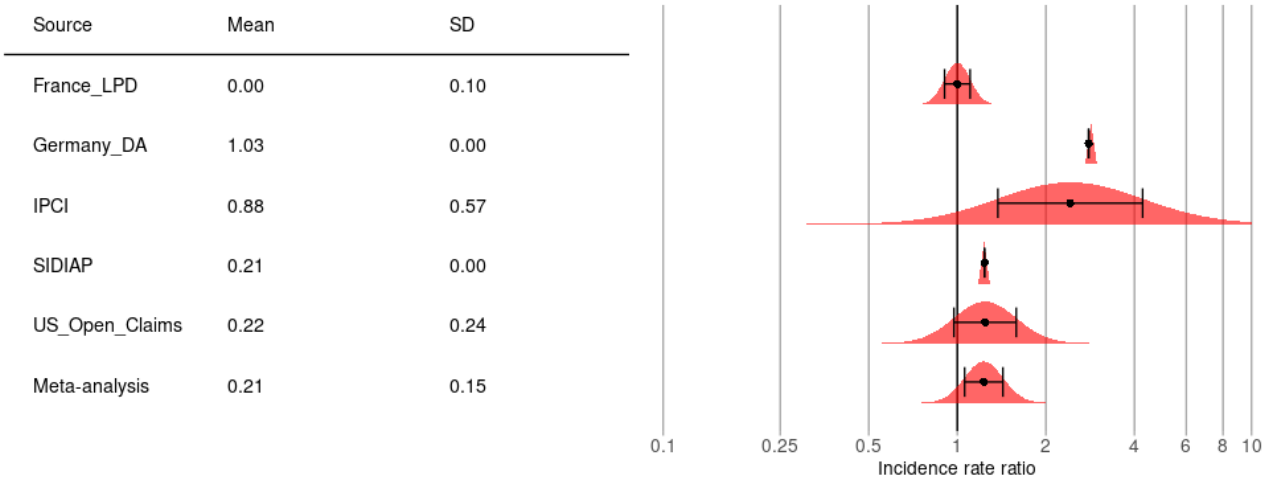
Intestinal infarction was studied in 2 databases, SIDIAP CMBD ES and IQVIA US Open Claims, with meta-analyses depicted in Figure 20. The resulting pooled estimate suggested in this case a lower risk associated with Janssen vs 1-dose Comirnaty, with a calibrated IRR of 0.37 [0.15-0.89].

Figure 20. Forest plot for the association between Janssen vs 1-dose Comirnaty and intestinal infarction



Given the obvious disparity between uncalibrated vs calibrated IRR in the analyses of ATE, with some of the meta-analytic estimates changing from significantly increased risk to no association, we show in Figure 21 a depiction of the distribution of systematic error in the meta-analysis of ATE in Janssen vs 1-dose Comirnaty. As observed in the figure, 4 out of 5 contributing databases (all but LPD France) showed fitted null distributions based on negative control outcomes falling to the right of the null effect (IRR>1). This shows the need for empirical calibration to account for such systematic error as proposed in our study protocol.

Figure 21. Fitted null distributions based on negative control outcome analyses of Janssen vs 1-dose Comirnaty in the meta-analysis for ATE



Regarding thrombosis with thrombocytopenia, Forest plots are depicted in Figures 22-24. Meta-analytic estimates were available for the association between Janssen and 1-dose Comirnaty and TTS DVT (calibrated IRR 1.83 [0.62-5.38], I2=0%), TTS VTE (calibrated IRR 2.26 (0.93-5.52, I2=0%), and TTS ATE (calibrated IRR 0.62 [0.20-1.98], I2=0%).

Figure 22. - Forest plot for the association between Janssen vs 1-dose Comirnaty and TTS DVT

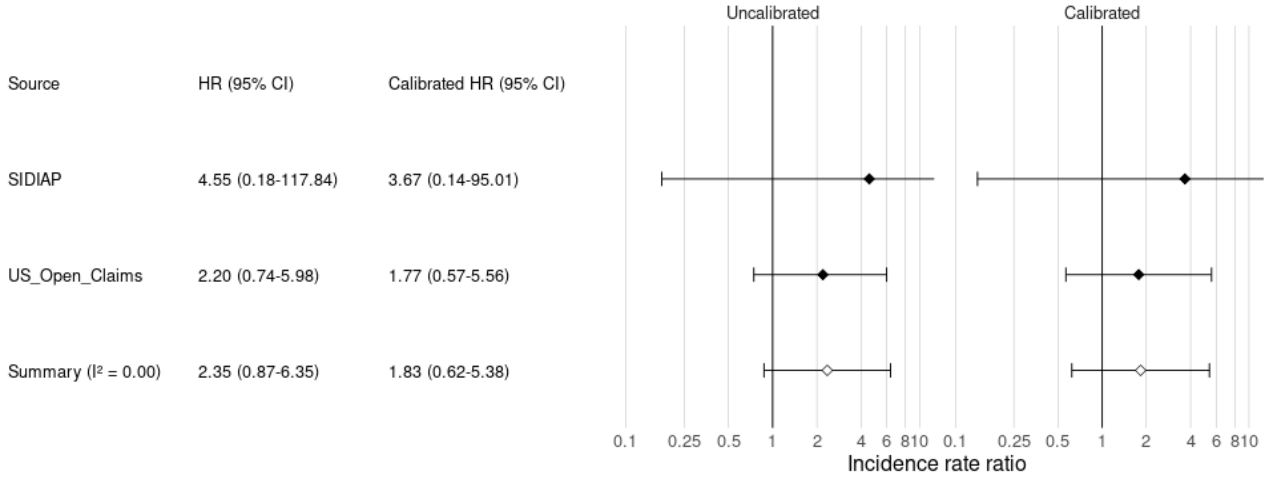


Figure 23. Forest plot for the association between Janssen vs 1-dose Comirnaty and TTS VTE

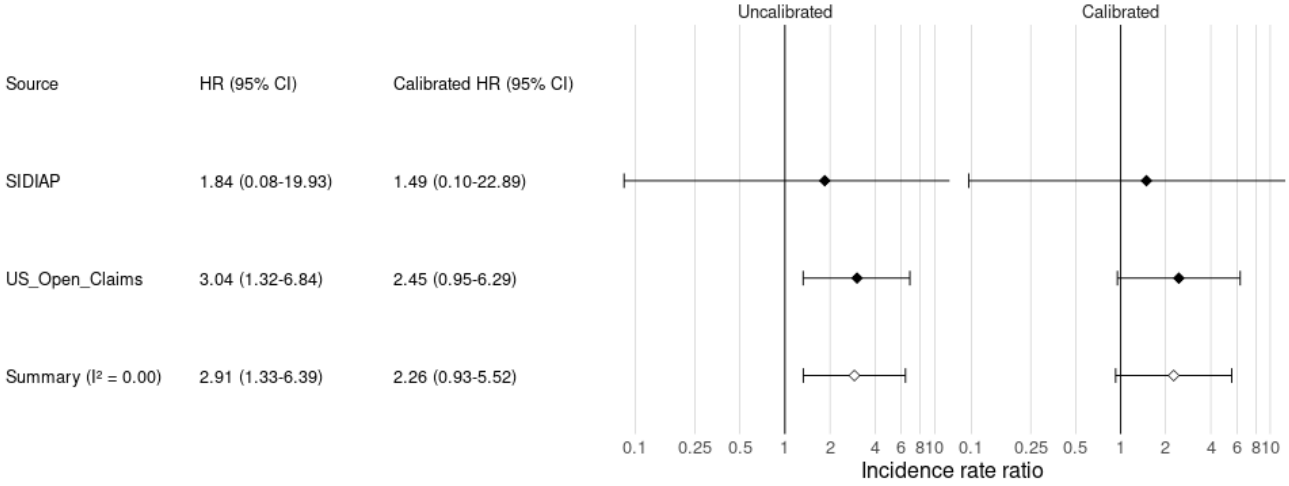
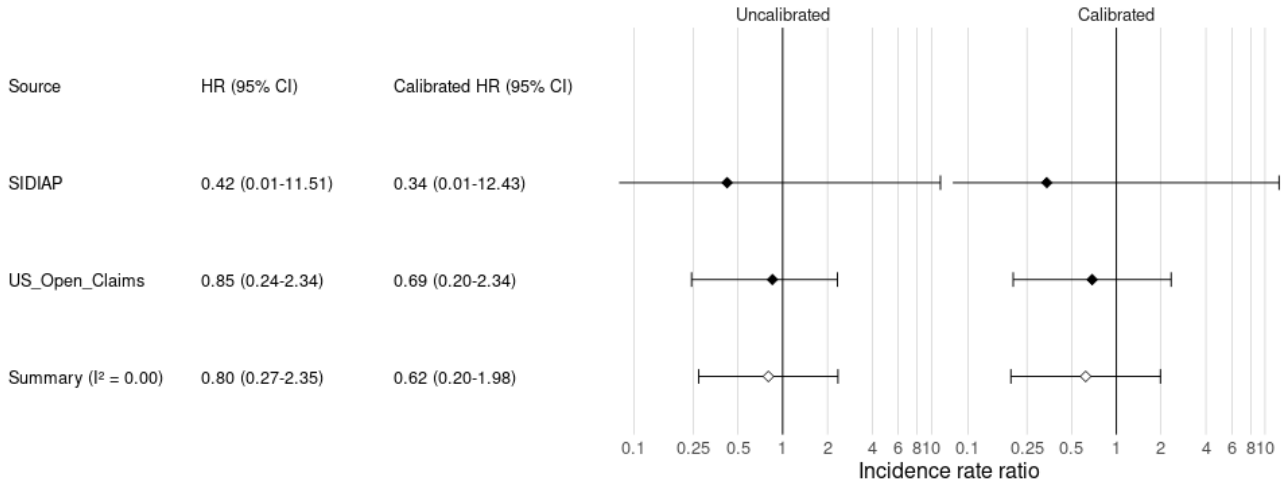


Figure 24. Forest plot for the association between Janssen vs 1-dose Comirnaty and TTS ATE



11.5 Sensitivity analyses

11.5.1 Alternative definitions of TTS: shorter time window or lower platelet count thresholds

Alternative definitions of TTS using a lower threshold for thrombocytopenia (<100,000 instead of <150,000) showed similar results to those obtained for the main definition when Vaxzevria 1-dose and Comirnaty 1-dose were compared in CPRD AURUM: calibrated IRR 1.29 [0.94-1.78] vs 1.29 [0.94-1.77] respectively. Similarly, TTS defined using a shorter time frame (5 days before/after thrombosis) resulted in a calibrated IRR 1.30 [0.95-1.79] for the same database-target-comparator.

As for the analysis of TTS VTE identified in the comparison between Janssen COVID-19 and Comirnaty 1-dose in IQVIA US Open Claims, the calibrated IRR based on a lower platelet count threshold (<100,000) resulted in a calibrated IRR of 2.45 [0.95-6.29], exactly the same as the original estimate based on a threshold of <150,000 platelets. The use of a shorter time window (5 days instead of 10) gave a calibrated IRR of 1.62 [0.56-4.68].

All the detailed results on these analyses, including N, incidence rates, and diagnostics for these alternative TTS definitions are available in our interactive web application.

11.5.2 Stratified analyses

As proposed per protocol, we attempted stratification by age, sex, and index month. Most of the stratified analyses did not pass diagnostics due to reduced sample size and power. The ones that passed diagnostics are reported in Figures 25-28.

For the analysis of Vaxzevria vs Comirnaty, these were based on CPRD AURUM data. No consistent or clear differential effects were observed across the strata. The potential associations observed with thrombocytopenia and TTS (any) seemed clearer in women and men respectively. Both showed a higher calibrated IRR in people aged 40-49 and 70-79, and in February 2021 (index month 2).

Figure 25. Calibrated IRR: stratified analyses of 1-dose Vaxzevria vs 1-dose Comirnaty in CPRD AURUM

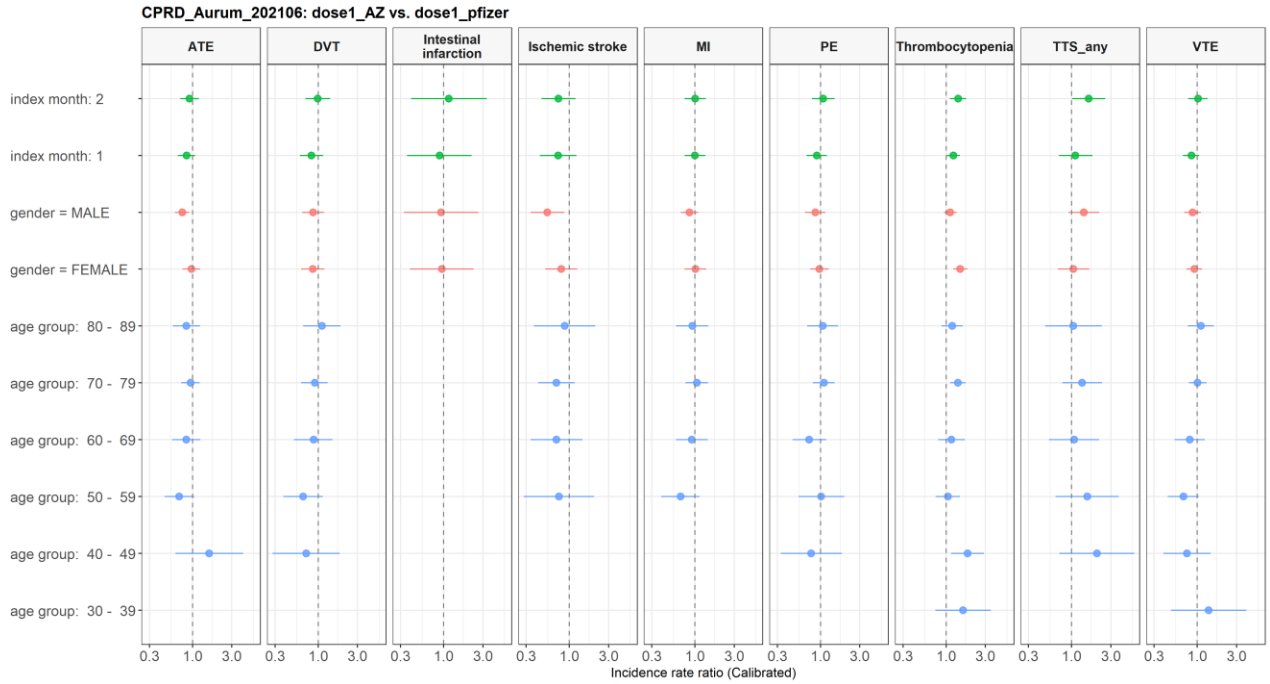
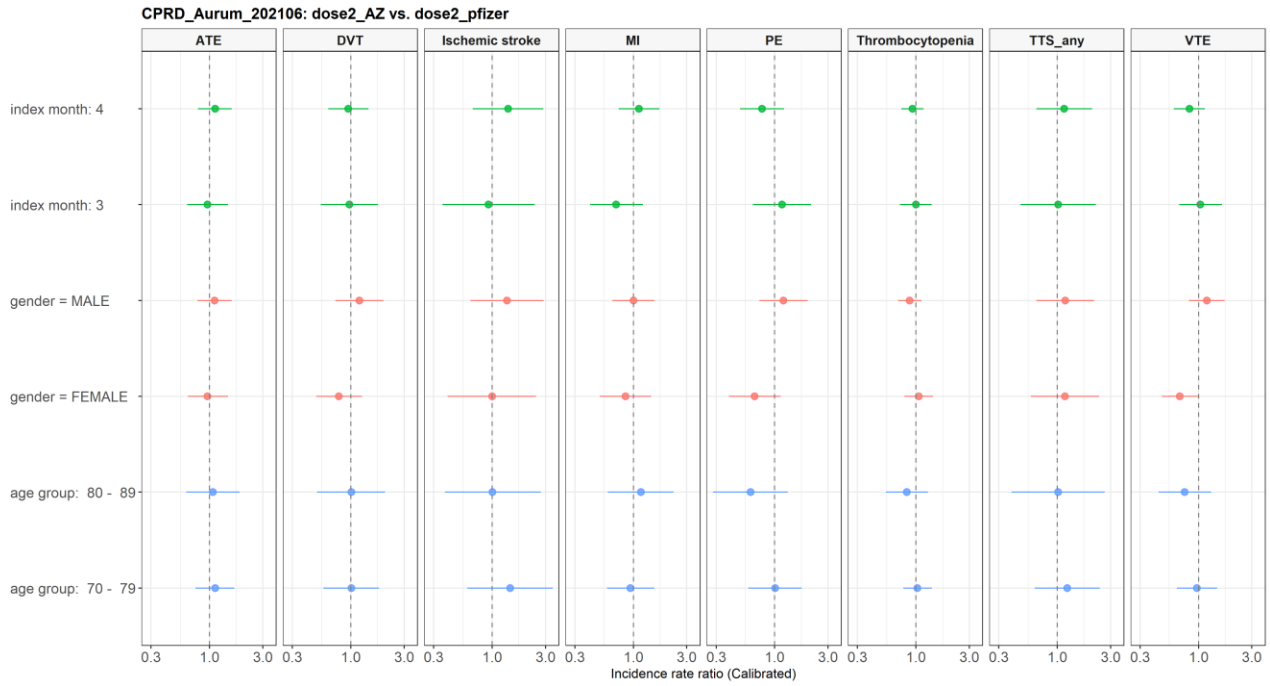


Figure 26. Calibrated IRR: stratified analyses of 2-dose Vaxzevria vs 2-dose Comirnaty in CPRD AURUM



As for the Janssen COVID-19 vaccine, no consistent change in effect size or pattern was identified across the analysed strata. A calibrated IRR>1 was observed for ATE specifically in the stratum of age 20-29 both in the comparison vs Comirnaty and vs Spikevax, and a calibrated IRR<1 in the age group 80-89 with the former. These results are not adjusted for multiple testing.

Figure 27. Calibrated IRR: stratified analyses of Janssen COVID-19 vs 1-dose Comirnaty in Open Claims

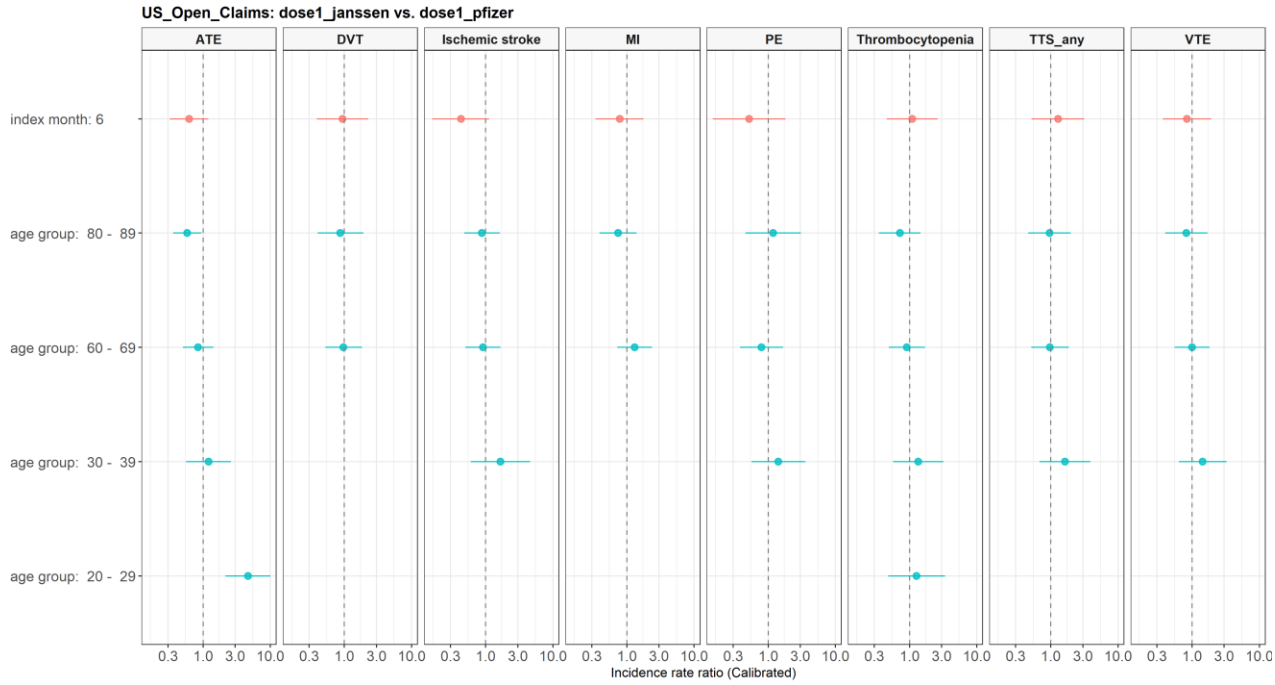
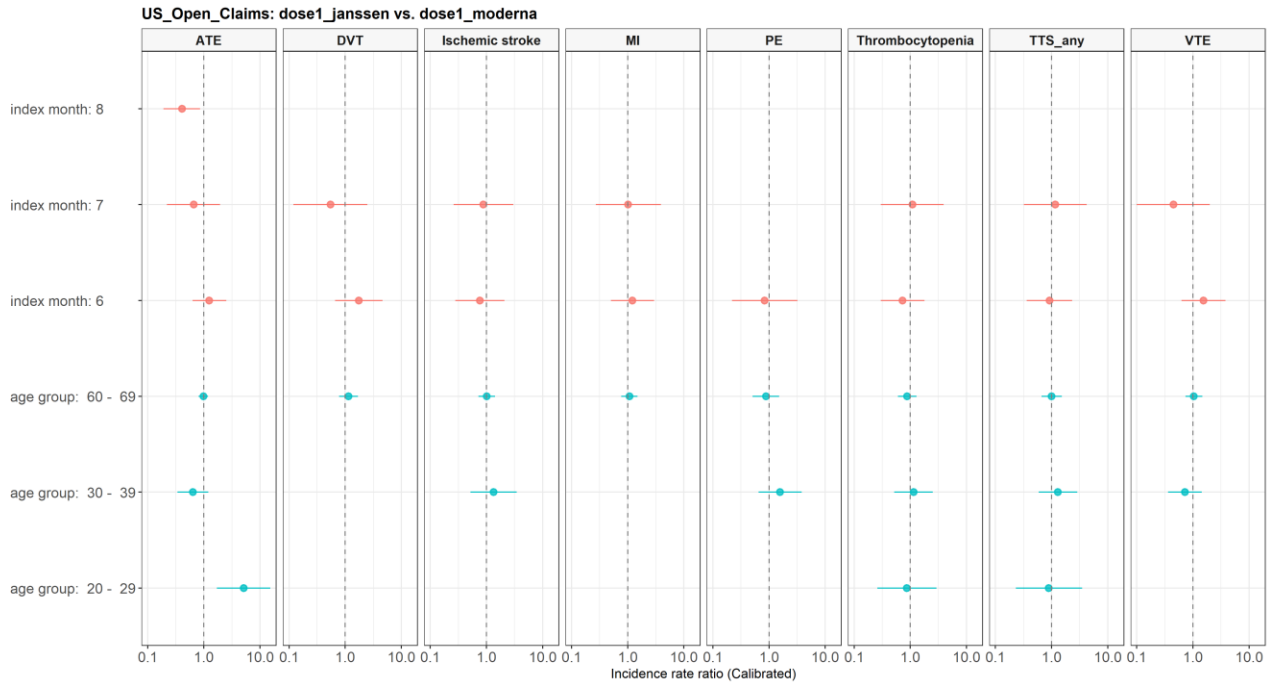


Figure 28. Calibrated IRR: stratified analyses of Janssen COVID-19 vs 1-dose Spikevax in Open Claims



12 Discussion

12.1 Key Findings

12.1.1 Objectives 1a and 2a

Two databases obtained complete information on vaccination status through linkage to national/regional registries: CPRD AURUM UK and SIDIAP ES. These were the only data sources used for Objectives 1a and 2a, as they were the only databases where unvaccinated status and/or time was reliably identified.

Despite good information on exposure, covariates and outcomes through linkage, both databases failed our proposed diagnostics in these analyses. Even after large-scale propensity score matching, very important confounders remained imbalanced when each vaccinated cohort was compared to the matched unvaccinated. Key confounders included age, comorbidity, cardiovascular history including for example atrial fibrillation or cerebrovascular disease, frailty, and other risk factors for thromboembolic disease and thrombocytopenia.

As pre-specified in our protocol, we did not complete these analyses to prevent the reporting of misleading data biased due to confounding by indication. We elaborate on potential plans future analyses and existing data on the study of vaccine vs no vaccine safety in subsequent sections.

12.1.2 Objective 1b: comparative safety related to TTS risk

Different countries of those contributing to the study used and implemented different guidelines for vaccination, resulting in different uses of the available vaccines. This led to the expected confounding by indication. As pre-specified per protocol, we used large scale PS matching to obtain cohorts of people vaccinated with adenovirus-based vaccines and match them to comparable subjects vaccinated with mRNA-based ones. The proposed three diagnostics (power, covariate balance, and systematic error) were then used to decide on what analyses were reliable enough to be completed.

Thrombocytopenia, one of the components of TTS, is relatively common, with rates post-vaccine ranging from just below 5/1,000 person-years to almost 10/10,000 person-years. Database-specific results were obtained for the comparison between Vaxzevria and Comirnaty vaccinees from CPRD AURUM UK and IQVIA DA Germany. A 30% increased risk was seen after a first dose of Vaxzevria in the UK data, but not replicated in Germany. The meta-analytic estimate, including information from France, Germany, Netherlands and the UK combined, was closer to the UK findings, with a 33% excess risk of thrombocytopenia associated with 1-dose Vaxzevria (compared to 1-dose Comirnaty). This increase risk was not seen after a second dose of these same vaccines. This apparent lack of association could be due to depletion of susceptible participants.

Any TTS, resulting from the combination of thrombocytopenia with any thrombosis (either VTE or ATE), was less common than thrombocytopenia alone, with rates post-vaccine ranging from 0.7/1,000 person-years to 3.1/1,000 person-years. Database-specific analyses suggested a possible 30% increased risk of any TTS following 1-dose Vaxzevria vs 1-dose Comirnaty in CPRD AURUM UK. The comparison between Janssen COVID-19 and first-dose Comirnaty or Spikevax in US health claims data did not replicate this finding. No meta-analytic estimate was available for this event, as only one database provided reliable results for each of the combinations here reported.

TTS VTE, resulting from the combination of VTE with thrombocytopenia, was rare at a rate post-vaccine ranging between 0.1 and 0.2/1,000 person-years. We found a trend towards an increased

risk in people receiving Janssen COVID-19 vs matched 1-dose Comirnaty recipients in IQVIA US Open Claims (calibrated IRR 2.45 [0.95-6.29]), with a similar but less accurate result seen for Janssen COVID-19 vs 1-dose Spikevax in the same database (calibrated IRR 1.92 [0.77-4.80]). Similar analyses of SIDIAP ES data were too underpowered, but meta-analyses resulted in a pooled effect like that seen in the IQVIA US Open Claims, with an approximate double risk of TTS VTE amongst users of Janssen COVID-19 compared to matched users of 1-dose Comirnaty. TTS VTE data were not available for the comparison of Vaxzevria vs Comirnaty or vs Spikevax due to limited statistical power and/or unreliable diagnostics.

The analysis of specific TTS VTE events, resulting from the combination of thrombocytopenia and specific events (e.g. DVT or PE) did not show consistent evidence of an increased risk of any of these in particular, although power was limited due to the rarity of these events.

TTS ATE was analysed only for the association between Janssen COVID-19 vs 1-dose Comirnaty in two databases, namely US health claims and Spanish primary care records linked to hospital admission data. No increased risk was seen for this comparison in either, with a pooled meta-analytic estimate of calibrated IRR 0.62 [0.20-1.98].

12.1.3 Objective 2b: comparative safety related to VTE or ATE risk

VTE is a relatively common event, with rates post-vaccine ranging from 2.5 to 4/1,000 person-years across cohorts and databases. The association between vaccine type and VTE was studied with successful diagnostics in data from the UK, Germany, Spain and the US. For the two former, no association was seen between 1-dose Vaxzevria vs 1-dose Comirnaty in the UK, but a trend towards an increased risk for this same comparison was seen in German data. Heterogeneity precluded the meta-analysis of these findings. Exposure to two doses of these same vaccines was more consistent, not showing any increased risk in any of the contributing databases. Reassuringly, no association was found between Janssen COVID-19 vs 1-dose Comirnaty or Spikevax and the risk of VTE post-vaccine in US or Spanish data.

DVT and PE were common enough to be studied separately, with rates post-vaccine ranging from 1.3 to 3.3/1,000 person-years and from 0.6 to 2.2/1,000 person-years respectively. For DVT, comparative safety results were obtained for 1-dose Vaxzevria vs 1-dose Comirnaty from the UK and Germany, with no consistency between them: whilst no association was noticed in the UK, a more than double risk was seen in Germany. A meta-analysis was not possible due to the observed heterogeneity (I2 of 86%). Exposure to two doses of these same vaccines was analysed only in UK data, with no differential risk of DVT noticed.

As for PE, no differential risk was observed after any of the studied vaccines, including 1- or 2-dose Vaxzevria vs Comirnaty in the UK and Germany, or after Janssen COVID-19 vs 1-dose Comirnaty or Spikevax in Spain or the US. The resulting meta-analytic estimates were consistent with this, with pooled calibrated IRR 0.96 [0.79-1.15] for 1-dose Vaxzevria vs 1-dose Comirnaty, and pooled calibrated IRR 1.17 [0.70-1.97] for the comparison between Janssen COVID-19 and 1-dose Comirnaty.

Rare VTE events under study included CVST and SVT. For CVST, meta-analytic estimates were available for 1-dose Vaxzevria vs Comirnaty, and for Janssen COVID-19 vs 1-dose Comirnaty. Both estimates were very inaccurate due to limited power, but showed a numerical imbalance in both cases, with pooled calibrated IRR 4.20 [0.17-106.08] and 2.23 [0.61-8.18] respectively. As for SVT, only US claims provided enough power, and showed a possible increased risk associated with Janssen COVID-19 vs 1-dose Comirnaty and vs 1-dose Spikevax. However, confidence intervals

were too wide and crossed the null, suggesting the need for additional data on this issue: calibrated IRR 1.46 [0.59-3.61] and 1.48 [0.60-3.65] respectively.

ATE as a composite of ischemic stroke and myocardial infarction was relatively common, with post-vaccine rates ranging from 2.5 to 15.8/1,000 person-years. Greater heterogeneity was seen for this event, with 2- and 3-fold higher rates noticed in the US health claims vs European data. Interestingly, a potential 15% relative reduction in risk of ATE was noticed amongst people who received 1-dose Vaxzevria compared to those receiving 1-dose Comirnaty, with a similar estimate seen in the UK and Germany, and a pooled calibrated IRR of 0.87 [0.75-1.01] favoring the former. No association was seen in the analysis of 2-dose Vaxzevria vs 2-dose Comirnaty in the UK, or in the analysis of Janssen vs 1-dose Comirnaty or Spikevax in Spain or the US. The meta-analytic calibrated IRR for ATE in the comparison of Janssen vs 1-dose Comirnaty was similar to that seen for 1-dose Vaxzevria, but with wider confidence intervals: 0.89 [0.58-1.37].

Post-vaccine MI was also relatively common, with rates ranging from 1.6 to 2.2/1,000 person-years in Europe, and up to 3.6/1,000 person-years in US health claims data. No association was found between vaccination with 1-dose Vaxzevria vs Comirnaty (meta-analytic calibrated IRR 0.96 (0.80-1.15]) or between Janssen COVID-19 vs Comirnaty (meta-analytic calibrated IRR 0.97 [0.61-1.53]), or vs Spikevax. The latter relied on US data only.

As for ischemic stroke, rates post-vaccine ranged from 0.4 to 3.3/1,000 person-years in Europe, and from 3.2 to 4.1/1,000 person-years in the US. No increased risk of ischemic stroke was seen in any of the contributing databases, or for any of the studied comparisons between adenovirus-based and mRNA-based vaccines.

Finally, less common ATE events studied included intestinal infarction. Only available with passed diagnostics from US health claims data, the rates of post-vaccine intestinal infarction were low at 0.2-0.3/1,000 person-years. Interestingly, we found a substantial reduction in relative risk of this event by about 65-70% following Janssen COVID-19 vs 1-dose Comirnaty or Spikevax. This signal was not exactly replicated in SIDIAP, where power diagnostics were not passed, but the pooled (meta-analytic) estimate showed a calibrated IRR 0.37 [0.15-0.89] for Janssen COVID-19 vs 1-dose Comirnaty.

12.2 Interpretation and research in context of previous knowledge

No previous analyses of vaccinated vs concomitant unvaccinated cohorts have been published to date, probably due to the difficulty of accounting for confounding in the analysis of vaccines with such high uptake. However, historical cohort analyses and self-controlled case series (SCCS) have provided an answer for this question using data from numerous countries and data sources.

SCCS analyses from linked UK data have suggested an increased risk of thrombocytopenia and VTE after Vaxzevria, and an elevated risk of CVST after both the Vaxzevria and Comirnaty vaccines [J Hippisley-Cox et al. BMJ 2021]. A separate record linkage study of hospital admissions data from England showed an excess risk of CVST and other thrombotic events after 1-dose Vaxzevria in adults aged under 65 years, but not in those aged 65 years or older, or after Comirnaty [Andrews NJ et al. Lancet Reg Health Eur 2022].

Our comparative safety analyses suggest an increased risk of thrombocytopenia following 1-dose Vaxzevria (vs Comirnaty), a potential increase in risk of TTS VTE following Janssen (vs mRNA vaccines), and a possible increase in risk of CVST following both vaccines. Historical comparison cohort data produced by our group and currently under review [preprint as E Burn et al. MedrXiv

2021] suggested an age-sex adjusted increased risk of thrombocytopenia following Vaxzevria but not after Comirnaty, in line with our comparative safety analyses.

Additionally, we noticed a possible 15% lower risk of ATE following Vaxzevria (vs Comirnaty). The UK-based SCCS by Hippisley-Cox et al found an increased risk of ATE after Comirnaty but not Vaxzevria. Combined with our findings, this would suggest a possible small increased risk of ATE following vaccination with Comirnaty (but not after adenovirus-based vaccines).

We did not find a consitent differential risk of VTE, DVT, PE, SVT, MI, or ischemic stroke with any of the studied vaccines and/or doses. This suggests that none of these events are causally associated with any of the studied vaccines.

12.3 Strengths and Limitations

The observational nature of our data limits our ability to disentangle causal associations. However, we used large-scale propensity score matching to adjust for observed confounding, and negative control outcomes and empirical calibration to account for potential residual (unobserved) confounders. We used manual review of the propensity score models after data-driven selection of covariates. The benefits of this approach are not well established, but this step led to the exclusion of potential instrumental variables including invitations to vaccination clinic/s and mobile text reminders to attend a vaccine centre.

In addition, the use of robust diagnostics precluded the analysis of database-target-comparator-outcome combinations that were limited by low statistical power (MDRR>5) or residual confounding by indication (covariate balance). Also, our assessment of systematic error based on the analysis of multiple negative control outcomes helped us identify and calibrate analyses with substantial residual bias. However, the use of these robust methods led to the exclusion of any of the planned analyses of vaccine vs no vaccine safety. Given the high uptake of COVID-19 vaccines and the use of mandatory vaccination guidelines by EU member states and around the world, it is likely that a cohort analysis like this would not be possible. Instead, SCCS analyses are probably best suited to disentangle within-person pre vs post-vaccine effects. However, SCCS methods have strong limitations that should be thoroughly tested before any results can be credible. Other methods like historical comparisons have also been used, but a recent study by our group has demonstrated their limitations, including a very high probability of false positive signals [X Li et al. Front Pharmacol].

Information bias is also a known limitation of real world data analyses like the ones reported in this report. Vaccine exposure data was highly reliable in at least two of the contributing data sources (UK and ES) due to linkage to national/regional vaccine registries, but less so in other databases where information depends on clinical coding. Given the use of community-based vaccination centres and campaigns, it is possible that some vaccine exposures were missed in our data from France, Germany, the Netherlands and the US. However, we are confident that people with a clinical record for a vaccination were indeed vaccinated, and expect that any related information bias would be non-differential for recipients of different vaccines after PS matching.

Information bias can also affect outcome ascertainment. We used robust methods for the creation and transportation of algorithms for the identification of all of the study events. However, previous research by our group demonstrates that TTS as identified in these data does not necessarily match the reports of post-vaccination immune-induced TTS in the literature [E Burn et al. PDS 2022]. These same reports suggested great heterogeneity in the proportion of thrombosis cases with associated platelet count measurements available across databases. In fact, most clinical guidelines

require the measurement of anti-platelet factor 4 (PF4) antibodies for the identification of vaccine-induced thrombosis with thrombocytopenia (VITT), not available in our data and possibly under-measured and under-recorded in most routine clinical data. It is therefore possible that our study results do not reflect the potential effect of vaccines on uncommon and hard to diagnose events like VITT.

Finally, our study was underpowered for some extremely rare events like CVST. Alternative analyses like for example propensity score stratification or inverse probability weighting could potentially increase statistical power, but possibly at the cost of increasing covariate imbalances. Weighting and stratification would also answer a potentially different clinical question, as they typically provide effect estimates based on the whole target population, whilst matching focuses on the "treated" (here those eligible for vaccination with adenovirus-based vaccines).

12.4 Conclusions

Confounding limited our ability to study the risk of TTS, VTE, or ATE in vaccinated vs unvaccinated subjects. Previous studies using alternative methods (SCCS and historical cohort analyses) have reported on this.

This is the largest study on the comparative safety of adenovirus- vs mRNA-based COVID-19 vaccines, including data from 5 European countries and the US and covering >4.4 million people exposed to at least 1 dose of Vaxzevria, over 10.1 million to Comirnaty, almost 5 million to Spikevax, and more than 1 million to Janssen COVID-19 vaccine.

Our analyses showed a 30% increased risk of thrombocytopenia following 1-dose Vaxzevria (vs 1-dose Comirnaty), a potential double risk of TTS-VTE following Janssen COVID-19 (vs 1-dose Comirnaty), and a possible 2-to-4-fold increased relative risk of CVST following Janssen COVID-19 or Vaxzevria. The latter needs further studies due to limited statistical power.

Conversely, we also noticed a 15% lower risk of ATE following 1-dose Vaxzevria (vs 1-dose Comirnaty), and a 65-70% reduced risk of intestinal infarction following Janssen COVID-19 (vs 1-dose Comirnaty or Spikevax). This could be related to a small increase in risk of ATE and intestinal infarction associated with mRNA-based COVID-19 vaccines, but warrants further research.

Finally, no consistent differential risk of DVT, PE, VTE, or SVT was noticed amongst people receiving adenovirus- vs mRNA-based COVID-19 vaccines.

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

Annex 3. Concept set for persons vaccinated against SARS-CoV-2

Please note, these concept sets will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

Sub concept sets for each type as well as brand of COVID-19 vaccine will be created from the relevant concept ID below.

Concept ID	Name	Vocabulary
59267100003	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
59267100002	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
592671000	bnt162b2 .23mg/1.8mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
80777027310	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
2470234	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	RxNorm
2470233	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML	RxNorm
2470232	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273	RxNorm
2468235	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	RxNorm
2468234	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Suspension	RxNorm
2468233	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Product	RxNorm
2468232	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML	RxNorm
2468231	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	RxNorm
2468230	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2	RxNorm
80777027399	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
807770273	cx-024414 .2mg/mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
39214411000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 1170 dose	dm+d
39326611000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials 100 dose	dm+d
39326811000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d

Concept ID	Name	Vocabulary
39214511000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 1170 dose 195 x 6 dose vials	dm+d
39327011000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials (Moderna, Inc) 100 dose 10 x 10 dose vials	dm+d
39326911000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d
39115611000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
39115311000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 6 dose	dm+d
39115711000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 6 dose	dm+d
39116111000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
59676058005	Janssen COVID-19 vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122210	AZD1222 Astrazeneca COVID-19 vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122215	azd1222 50000000000[VP]/.5mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
59267100001	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
91303	Janssen Covid-19 Vaccine	CPT4
91302	AstraZeneca Covid-19 Vaccine	CPT4
91301	Moderna Covid-19 Vaccine	CPT4
91300	Pfizer-Biontech Covid-19 Vaccine	CPT4
0022A	AstraZeneca Covid-19 Vaccine Administration - Second Dose	CPT4
0021A	AstraZeneca Covid-19 Vaccine Administration - First Dose	CPT4
0031A	Janssen Covid-19 Vaccine Administration	CPT4
0012A	Moderna Covid-19 Vaccine Administration - Second Dose	CPT4
0011A	Moderna Covid-19 Vaccine Administration - First Dose	CPT4
0002A	Pfizer-Biontech Covid-19 Vaccine Administration - Second Dose	CPT4
0001A	Pfizer-Biontech Covid-19 Vaccine Administration - First Dose	CPT4
208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	CVX
207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose	CVX

Concept ID	Name	Vocabulary
210	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	CVX
212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	CVX

Annex 4. Preliminary lists of included concepts for study outcomes

Please note, these concept set will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

A4.1. Cerebral venous sinus thrombosis (CVST)

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4102202	Cerebral venous sinus thrombosis	SNOMED	FALSE	FALSE
4048786	Cerebral venous thrombosis of sigmoid sinus	SNOMED	FALSE	FALSE
4043735	Cerebral venous thrombosis of straight sinus	SNOMED	FALSE	FALSE
4111713	Non-pyogenic venous sinus thrombosis	SNOMED	FALSE	FALSE
314667	Nonpyogenic thrombosis of intracranial venous sinus	SNOMED	FALSE	FALSE
4116206	Septic thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4121335	Septic thrombophlebitis of lateral sinus	SNOMED	FALSE	FALSE
4119136	Septic thrombophlebitis of sagittal sinus	SNOMED	FALSE	FALSE
4041680	Septic thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100225	Thrombophlebitis lateral venous sinus	SNOMED	FALSE	FALSE
4217471	Thrombophlebitis of basilar sinus	SNOMED	FALSE	FALSE
4104695	Thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4167985	Thrombophlebitis of inferior sagittal sinus	SNOMED	FALSE	FALSE
764714	Thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100224	Thrombophlebitis of superior longitudinal venous sinus	SNOMED	FALSE	FALSE
4098706	Thrombophlebitis of superior sagittal sinus	SNOMED	FALSE	FALSE
4277833	Thrombophlebitis of torcular Herophili	SNOMED	FALSE	FALSE
764710	Thrombophlebitis of transverse sinus	SNOMED	FALSE	FALSE
4228209	Thrombosis of basilar sinus	SNOMED	FALSE	FALSE
4234264	Thrombosis of cavernous venous sinus	SNOMED	FALSE	FALSE
4048890	Thrombosis of inferior sagittal sinus	SNOMED	FALSE	FALSE
4057329	Thrombosis of lateral venous sinus	SNOMED	FALSE	FALSE
4102203	Thrombosis of superior longitudinal sinus	SNOMED	FALSE	FALSE
4290940	Thrombosis of superior sagittal sinus	SNOMED	FALSE	FALSE
4079905	Thrombosis of torcular Herophili	SNOMED	FALSE	FALSE

4105338	Thrombosis transverse sinus	SNOMED	FALSE	FALSE

A4.2. Deep vein thrombosis – narrow

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
762047	Acute bilateral thrombosis of subclavian veins	SNOMED	FALSE	FALSE
762148	Acute deep vein thrombosis of bilateral iliac veins	SNOMED	FALSE	FALSE
761444	Acute deep vein thrombosis of bilateral lower limbs following coronary artery bypass graft	SNOMED	FALSE	FALSE
35616028	Acute deep vein thrombosis of left iliac vein	SNOMED	FALSE	FALSE
35615035	Acute deep vein thrombosis of left lower limb following procedure	SNOMED	FALSE	FALSE
761416	Acute deep vein thrombosis of left upper limb following coronary artery bypass graft	SNOMED	FALSE	FALSE
35615031	Acute deep vein thrombosis of left upper limb following procedure	SNOMED	FALSE	FALSE
43531681	Acute deep vein thrombosis of lower limb	SNOMED	FALSE	FALSE
35616027	Acute deep vein thrombosis of right iliac vein	SNOMED	FALSE	FALSE
35615034	Acute deep vein thrombosis of right lower limb following procedure	SNOMED	FALSE	FALSE
761415	Acute deep vein thrombosis of right upper limb following coronary artery bypass graft	SNOMED	FALSE	FALSE
35615030	Acute deep vein thrombosis of right upper limb following procedure	SNOMED	FALSE	FALSE
44782746	Acute deep venous thrombosis	SNOMED	FALSE	FALSE
44782751	Acute deep venous thrombosis of axillary vein	SNOMED	FALSE	FALSE
762008	Acute deep venous thrombosis of bilateral axillary veins	SNOMED	FALSE	FALSE
760875	Acute deep venous thrombosis of bilateral calves	SNOMED	FALSE	FALSE
765155	Acute deep venous thrombosis of bilateral ileofemoral veins	SNOMED	FALSE	FALSE
762017	Acute deep venous thrombosis of bilateral internal jugular veins	SNOMED	FALSE	FALSE
762417	Acute deep venous thrombosis of bilateral legs	SNOMED	FALSE	FALSE
762020	Acute deep venous thrombosis of bilateral popliteal veins	SNOMED	FALSE	FALSE
765546	Acute deep venous thrombosis of bilateral tibial veins	SNOMED	FALSE	FALSE
762004	Acute deep venous thrombosis of both upper extremities	SNOMED	FALSE	FALSE
44782742	Acute deep venous thrombosis of calf	SNOMED	FALSE	FALSE
44782747	Acute deep venous thrombosis of femoral vein	SNOMED	FALSE	FALSE
762015	Acute deep venous thrombosis of ileofemoral vein of left leg	SNOMED	FALSE	FALSE
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity	SNOMED	FALSE	FALSE
44782748	Acute deep venous thrombosis of iliofemoral vein	SNOMED	FALSE	FALSE
44782752	Acute deep venous thrombosis of internal jugular vein	SNOMED	FALSE	FALSE
762009	Acute deep venous thrombosis of left axillary vein	SNOMED	FALSE	FALSE
760876	Acute deep venous thrombosis of left calf	SNOMED	FALSE	FALSE
765540	Acute deep venous thrombosis of left femoral vein	SNOMED	FALSE	FALSE
765922	Acute deep venous thrombosis of left internal jugular vein	SNOMED	FALSE	FALSE
762418	Acute deep venous thrombosis of left lower extremity	SNOMED	FALSE	FALSE

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
765537	Acute deep venous thrombosis of left upper extremity	SNOMED	FALSE	FALSE
44782767	Acute deep venous thrombosis of lower extremity as complication of procedure	SNOMED	FALSE	FALSE
46270071	Acute deep venous thrombosis of lower limb due to coronary artery bypass grafting	SNOMED	FALSE	FALSE
762022	Acute deep venous thrombosis of politeal vein of right leg	SNOMED	FALSE	FALSE
44782743	Acute deep venous thrombosis of popliteal vein	SNOMED	FALSE	FALSE
762021	Acute deep venous thrombosis of popliteal vein of left leg	SNOMED	FALSE	FALSE
762010	Acute deep venous thrombosis of right axillary vein	SNOMED	FALSE	FALSE
760877	Acute deep venous thrombosis of right calf	SNOMED	FALSE	FALSE
762013	Acute deep venous thrombosis of right femoral vein	SNOMED	FALSE	FALSE
762018	Acute deep venous thrombosis of right internal jugular vein	SNOMED	FALSE	FALSE
762419	Acute deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
762005	Acute deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE
44782745	Acute deep venous thrombosis of thigh	SNOMED	FALSE	FALSE
44782744	Acute deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
762026	Acute deep venous thrombosis of tibial vein of left leg	SNOMED	FALSE	FALSE
765156	Acute deep venous thrombosis of tibial vein of right leg	SNOMED	FALSE	FALSE
44782421	Acute deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft	SNOMED	FALSE	FALSE
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure	SNOMED	FALSE	FALSE
762048	Acute thrombosis of left subclavian vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
762049	Acute thrombosis of right subclavian vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
44782762	Acute thrombosis of subclavian vein	SNOMED	FALSE	FALSE
37109253	Bilateral acute deep vein thrombosis of femoral veins	SNOMED	FALSE	FALSE
40478951	Bilateral deep vein thrombosis of lower extremities	SNOMED	FALSE	FALSE
4046884	Deep vein thrombosis of leg related to air travel	SNOMED	FALSE	FALSE
4133004	Deep venous thrombosis	SNOMED	FALSE	FALSE
4181315	Deep venous thrombosis associated with coronary artery bypass graft	SNOMED	FALSE	FALSE
45773536	Deep venous thrombosis of femoropopliteal vein	SNOMED	FALSE	FALSE
763942	Deep venous thrombosis of left lower extremity	SNOMED	FALSE	FALSE
761980	Deep venous thrombosis of left upper extremity	SNOMED	FALSE	FALSE
443537	Deep venous thrombosis of lower extremity	SNOMED	FALSE	FALSE
4133975	Deep venous thrombosis of pelvic vein	SNOMED	FALSE	FALSE
40480555	Deep venous thrombosis of peroneal vein	SNOMED	FALSE	FALSE
4322565	Deep venous thrombosis of profunda femoris vein	SNOMED	FALSE	FALSE
763941	Deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
761928	Deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4207899	Deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
4028057	Deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
193512	Embolism and thrombosis of the renal vein	SNOMED	FALSE	FALSE
435565	Embolism and thrombosis of the vena cava	SNOMED	FALSE	FALSE
4119760	Iliofemoral deep vein thrombosis	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4281689	Phlegmasia alba dolens	SNOMED	FALSE	FALSE
4284538	Phlegmasia cerulea dolens	SNOMED	FALSE	FALSE
4309333	Postoperative deep vein thrombosis	SNOMED	FALSE	FALSE
46285905	Provoked deep vein thrombosis	SNOMED	FALSE	FALSE
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
42538533	Thrombosis of iliac vein	SNOMED	FALSE	FALSE
44811347	Thrombosis of internal jugular vein	SNOMED	FALSE	FALSE
765049	Thrombosis of left peroneal vein	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4203836	Thrombosis of subclavian vein	SNOMED	FALSE	FALSE
4175649	Thrombosis of the popliteal vein	SNOMED	FALSE	FALSE
4153353	Traumatic thrombosis of axillary vein	SNOMED	FALSE	FALSE
46285904	Unprovoked deep vein thrombosis	SNOMED	FALSE	FALSE
4221821	Thrombophlebitis of deep veins of lower extremity	SNOMED	FALSE	FALSE
46271900	Recurrent deep vein thrombosis	SNOMED	FALSE	FALSE
4189004	Deep vein thrombosis of leg related to intravenous drug use	SNOMED	FALSE	FALSE

A4.3. SVT

- **Splenic vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE

- **Splanchnic Vein Thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE

196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4092406	Portal thrombophlebitis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE

- **Portal vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE

- **Mesenteric vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE

- **Visceral venous thrombosis or obstruction**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
35624285	Complete obstruction of hepatic portal vein	SNOMED	FALSE	FALSE
4301208	Hepatic vein thrombosis	SNOMED	FALSE	FALSE
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome	SNOMED	FALSE	FALSE
37109927	Obstruction of visceral vein	SNOMED	FALSE	FALSE
4238060	Portal vein obstruction	SNOMED	FALSE	FALSE
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
4277276	Veno-occlusive disease of the liver	SNOMED	FALSE	FALSE
37111372	Visceral venous thrombosis	SNOMED	FALSE	FALSE
36712891	Chronic thrombosis of splenic vein	SNOMED	FALSE	FALSE

A4.4. Pulmonary embolism

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4120091	Acute massive pulmonary embolism	SNOMED	FALSE	FALSE
45768439	Acute pulmonary embolism	SNOMED	FALSE	FALSE
45768888	Acute pulmonary thromboembolism	SNOMED	FALSE	FALSE
4309039	Hemorrhagic pulmonary infarction	SNOMED	FALSE	FALSE
762808	Infarction of lung due to embolus	SNOMED	FALSE	FALSE
40480461	Infarction of lung due to iatrogenic pulmonary embolism	SNOMED	FALSE	FALSE
4108681	Postoperative pulmonary embolus	SNOMED	FALSE	FALSE
4091708	Pulmonary air embolism	SNOMED	FALSE	FALSE
440417	Pulmonary embolism	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
37016922	Pulmonary embolism on long-term anticoagulation therapy	SNOMED	FALSE	FALSE
43530605	Pulmonary embolism with pulmonary infarction	SNOMED	FALSE	FALSE
4119608	Pulmonary fat embolism	SNOMED	FALSE	FALSE
254662	Pulmonary infarction	SNOMED	FALSE	FALSE
4253796	Pulmonary microemboli	SNOMED	FALSE	FALSE
45766471	Pulmonary oil microembolism	SNOMED	FALSE	FALSE
4121618	Pulmonary thromboembolism	SNOMED	FALSE	FALSE
4119610	Pulmonary tumor embolism	SNOMED	FALSE	FALSE
4119607	Subacute massive pulmonary embolism	SNOMED	FALSE	FALSE
4119609	Subacute pulmonary fat embolism	SNOMED	FALSE	FALSE
4236271	Recurrent pulmonary embolism	SNOMED	FALSE	FALSE

A4.5. Thrombocytopenia

- Platelet measurement

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
3007461	Platelets [#/volume] in Blood	LOINC	FALSE	TRUE
3031586	Platelets [#/volume] in Blood by Estimate	LOINC	FALSE	TRUE
3024929	Platelets [#/volume] in Blood by Automated count	LOINC	FALSE	TRUE
3039827	Platelets [#/volume] in Body fluid by Automated count	LOINC	FALSE	TRUE
3024386	Platelet mean volume [Entitic volume] in Blood by Rees-Ecker	LOINC	FALSE	TRUE
4267147	Platelet count	SNOMED	FALSE	TRUE
37393863	Platelet count	SNOMED	FALSE	TRUE

- Thrombocytopenia diagnosis

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
37397537	Beta thalassemia X-linked thrombocytopenia syndrome	SNOMED	FALSE	FALSE
432870	Thrombocytopenic disorder	SNOMED	FALSE	FALSE
46272950	Thrombocytopathy, asplenia and miosis	SNOMED	FALSE	FALSE
44782445	Thrombocytopenia due to alcohol	SNOMED	FALSE	FALSE
42536958	Pancytopenia caused by medication	SNOMED	FALSE	FALSE
40321716	Secondary thrombocytopenia	SNOMED	FALSE	FALSE
37312165	Atypical hemolytic uremic syndrome	SNOMED	FALSE	FALSE
37209558	Pancytopenia caused by immunosuppressant	SNOMED	FALSE	FALSE
37204551	Hereditary isolated aplastic anemia	SNOMED	FALSE	FALSE
37204548	Hereditary thrombocytopenia with normal platelets	SNOMED	FALSE	FALSE
37204520	Bleeding diathesis due to thromboxane synthesis deficiency	SNOMED	FALSE	FALSE
37204478	Pancytopenia due to IKZF1 mutations	SNOMED	FALSE	FALSE
37117164	Revesz syndrome	SNOMED	FALSE	FALSE
37116398	Thyrocerebrorenal syndrome	SNOMED	FALSE	FALSE
37110394	Isolated thrombocytopenia	SNOMED	FALSE	FALSE
37019055	Aplastic anemia co-occurrent with human immunodeficiency virus infection	SNOMED	FALSE	FALSE
37018663	Thrombocytopenia co-occurrent and due to alcoholism	SNOMED	FALSE	FALSE
37017607	Antibody mediated acquired pure red cell aplasia caused by erythropoiesis stimulating agent	SNOMED	FALSE	FALSE
37017165	GATA binding protein 1 related thrombocytopenia with dyserythropoiesis	SNOMED	FALSE	FALSE
37016797	MYH9 related disease	SNOMED	FALSE	FALSE
37016151	Aplastic anemia caused by antineoplastic agent	SNOMED	FALSE	FALSE
36717326	DK phocomelia syndrome	SNOMED	FALSE	FALSE
36716406	Severe fever with thrombocytopenia syndrome virus	SNOMED	FALSE	FALSE
36716047	Radioulnar synostosis with amegakaryocytic thrombocytopenia syndrome	SNOMED	FALSE	FALSE
36715586	Refractory thrombocytopenia	SNOMED	FALSE	FALSE
36715053	Autosomal dominant macrothrombocytopenia	SNOMED	FALSE	FALSE
36713970	WT limb blood syndrome	SNOMED	FALSE	FALSE
36713443	MYH9 macrothrombocytopenia syndrome	SNOMED	FALSE	FALSE
36713112	Pancytopenia due to antineoplastic chemotherapy	SNOMED	FALSE	FALSE
36674972	Macrothrombocytopenia with mitral valve insufficiency	SNOMED	FALSE	FALSE
36674474	Pancytopenia with developmental delay syndrome	SNOMED	FALSE	FALSE
35625536	Ataxia pancytopenia syndrome	SNOMED	FALSE	FALSE
35623407	Adult pure red cell aplasia	SNOMED	FALSE	FALSE
4345236	Parvoviral aplastic crisis	SNOMED	FALSE	FALSE
4338386	Thrombocytopenia due to non-immune destruction	SNOMED	FALSE	FALSE
4316372	HELLP syndrome	SNOMED	FALSE	FALSE

4314802	Kasabach-Merritt syndrome	SNOMED	FALSE	FALSE
4311682	Radial aplasia-thrombocytopenia syndrome	SNOMED	FALSE	FALSE
4305588	Doan-Wright syndrome	SNOMED	FALSE	FALSE
4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4301128	Thrombocytopenia due to diminished platelet production	SNOMED	FALSE	FALSE
4300464	Wiskott-Aldrich autosomal dominant variant syndrome	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4298690	Immunologic aplastic anemia	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4292425	Sex-linked thrombocytopenia	SNOMED	FALSE	FALSE
4272928	Thrombocytopenia due to hypersplenism	SNOMED	FALSE	FALSE
4264464	Mediterranean macrothrombocytopenia	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4239484	Acquired pancytopenia	SNOMED	FALSE	FALSE
4235220	Hereditary thrombocytopenic disorder	SNOMED	FALSE	FALSE
4234973	Chronic acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4233407	Megakaryocytic aplasia	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4226905	Thrombocytopenia associated with AIDS	SNOMED	FALSE	FALSE
4225810	Aplastic anemia associated with AIDS	SNOMED	FALSE	FALSE
4219476	Thrombocytopenia due to defective platelet production	SNOMED	FALSE	FALSE
4218171	Uremic thrombocytopenia	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4211348	Aplastic anemia associated with pancreatitis	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4197574	Dilutional thrombocytopenia	SNOMED	FALSE	FALSE
4188208	Estren-Dameshek anemia	SNOMED	FALSE	FALSE
4186108	Aplastic anemia associated with metabolic alteration	SNOMED	FALSE	FALSE
4185078	Bernard Soulier syndrome	SNOMED	FALSE	FALSE
4184758	Acquired aplastic anemia	SNOMED	FALSE	FALSE
4184200	Secondary aplastic anemia	SNOMED	FALSE	FALSE
4177177	Cellular immunologic aplastic anemia	SNOMED	FALSE	FALSE
4173278	Thrombocytopenia due to blood loss	SNOMED	FALSE	FALSE
4172008	Cyclic thrombocytopenia	SNOMED	FALSE	FALSE
4166754	Perinatal thrombocytopenia	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4159749	Idiopathic maternal thrombocytopenia	SNOMED	FALSE	FALSE
4159736	Radiation thrombocytopenia	SNOMED	FALSE	FALSE
4156233	Thrombocytopenia due to sequestration	SNOMED	FALSE	FALSE

4148471	Fanconi’s anemia	SNOMED	FALSE	FALSE
4147049	Thrombocytopenia due to extracorporeal circulation	SNOMED	FALSE	FALSE
4146088	Aplastic anemia due to drugs	SNOMED	FALSE	FALSE
4146086	Constitutional aplastic anemia with malformation	SNOMED	FALSE	FALSE
4145458	Thrombocytopenia due to hypothermia	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4139555	Thrombocytopenia due to massive blood transfusion	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133981	Benign gestational thrombocytopenia	SNOMED	FALSE	FALSE
4125496	Pure red cell aplasia, acquired	SNOMED	FALSE	FALSE
4125494	Pancytopenia with pancreatitis	SNOMED	FALSE	FALSE
4123076	Montreal platelet syndrome	SNOMED	FALSE	FALSE
4123075	May-Hegglin anomaly	SNOMED	FALSE	FALSE
4123074	Megakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4121265	Mediterranean thrombocytopenia	SNOMED	FALSE	FALSE
4121264	Epstein syndrome	SNOMED	FALSE	FALSE
4120620	Amegakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4101603	Thrombocytopenia due to extracorporeal circulation of blood	SNOMED	FALSE	FALSE
4101583	Aplastic anemia due to infection	SNOMED	FALSE	FALSE
4101582	Aplastic anemia due to chronic disease	SNOMED	FALSE	FALSE
4100998	Aplastic anemia due to toxic cause	SNOMED	FALSE	FALSE
4098148	Thrombocytopenia due to drugs	SNOMED	FALSE	FALSE
4098145	Idiopathic aplastic anemia	SNOMED	FALSE	FALSE
4098028	Transient acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4098027	Aplastic anemia due to radiation	SNOMED	FALSE	FALSE
4082738	Autoimmune pancytopenia	SNOMED	FALSE	FALSE
4077348	Pancytopenia-dysmelia	SNOMED	FALSE	FALSE
4031699	Humoral immunologic aplastic anemia	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE
4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
441264	Primary thrombocytopenia	SNOMED	FALSE	FALSE
440982	Wiskott-Aldrich syndrome	SNOMED	FALSE	FALSE
440372	Acquired thrombocytopenia	SNOMED	FALSE	FALSE

436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
432881	Pancytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
140681	Constitutional aplastic anemia	SNOMED	FALSE	FALSE
138723	Acquired red cell aplasia	SNOMED	FALSE	FALSE
137829	Aplastic anemia	SNOMED	FALSE	FALSE

- Thrombocytopenic purpura

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE
4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
313800	Thrombotic microangiopathy	SNOMED	FALSE	FALSE

- Immune thrombocytopenia

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE

4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE

A4.6. Ischemic stroke

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4045735	Anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4031045	Anterior choroidal artery syndrome	SNOMED	FALSE	FALSE
761110	Bilateral cerebral infarction due to precererbral arterial occlusion	SNOMED	FALSE	FALSE
4110189	Cerebral infarct due to thrombosis of precerebral arteries	SNOMED	FALSE	FALSE
443454	Cerebral infarction	SNOMED	FALSE	FALSE
762951	Cerebral infarction due to anterior cerebral artery occlusion	SNOMED	FALSE	FALSE
765515	Cerebral infarction due to basilar artery stenosis	SNOMED	FALSE	FALSE
43530683	Cerebral infarction due to carotid artery occlusion	SNOMED	FALSE	FALSE
762933	Cerebral infarction due to cerebral artery occlusion	SNOMED	FALSE	FALSE
762937	Cerebral infarction due to cerebral venous thrombosis	SNOMED	FALSE	FALSE
4111714	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic	SNOMED	FALSE	FALSE
4108356	Cerebral infarction due to embolism of cerebral arteries	SNOMED	FALSE	FALSE
45772786	Cerebral infarction due to embolism of middle cerebral artery	SNOMED	FALSE	FALSE
4110190	Cerebral infarction due to embolism of precerebral arteries	SNOMED	FALSE	FALSE
762935	Cerebral infarction due to internal carotid artery occlusion	SNOMED	FALSE	FALSE
763015	Cerebral infarction due to middle cerebral artery occlusion	SNOMED	FALSE	FALSE
46273649	Cerebral infarction due to occlusion of basilar artery	SNOMED	FALSE	FALSE
35610084	Cerebral infarction due to occlusion of cerebral artery	SNOMED	FALSE	FALSE
46270031	Cerebral infarction due to occlusion of precerebral artery	SNOMED	FALSE	FALSE
762934	Cerebral infarction due to posterior cerebral artery occlusion	SNOMED	FALSE	FALSE
43531607	Cerebral infarction due to stenosis of carotid artery	SNOMED	FALSE	FALSE
35610085	Cerebral infarction due to stenosis of cerebral artery	SNOMED	FALSE	FALSE
46270381	Cerebral infarction due to stenosis of precerebral artery	SNOMED	FALSE	FALSE
4110192	Cerebral infarction due to thrombosis of cerebral arteries	SNOMED	FALSE	FALSE
45767658	Cerebral infarction due to thrombosis of middle cerebral artery	SNOMED	FALSE	FALSE
44782773	Cerebral infarction due to vertebral artery occlusion	SNOMED	FALSE	FALSE
46270380	Cerebral infarction due to vertebral artery stenosis	SNOMED	FALSE	FALSE
37110678	Cerebral ischemic stroke due to occlusion of extracranial large artery	SNOMED	FALSE	FALSE
37110679	Cerebral ischemic stroke due to stenosis of extracranial large artery	SNOMED	FALSE	FALSE
4043731	Infarction - precerebral	SNOMED	FALSE	FALSE

4131383	Infarction of basal ganglia	SNOMED	FALSE	FALSE
4046237	Infarction of optic radiation	SNOMED	FALSE	FALSE
4119140	Infarction of visual cortex	SNOMED	FALSE	FALSE
4141405	Left sided cerebral infarction	SNOMED	FALSE	FALSE
37116473	Multifocal cerebral infarction due to and following procedure on cardiovascular system	SNOMED	FALSE	FALSE
4077086	Occipital cerebral infarction	SNOMED	FALSE	FALSE
4046359	Partial anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4319146	Pituitary infarction	SNOMED	FALSE	FALSE
4146185	Right sided cerebral infarction	SNOMED	FALSE	FALSE
36717605	Silent cerebral infarct	SNOMED	FALSE	FALSE
4142739	Thalamic infarction	SNOMED	FALSE	FALSE
4046358	Total anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
372924	Cerebral artery occlusion	SNOMED	FALSE	FALSE

A4.7. Myocardial infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119457	Acute Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119943	Acute Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE
4121464	Acute Q wave infarction - inferior	SNOMED	FALSE	FALSE
4121465	Acute Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4124684	Acute Q wave infarction - lateral	SNOMED	FALSE	FALSE
4119948	Acute Q wave infarction - widespread	SNOMED	FALSE	FALSE
4126801	Acute Q wave myocardial infarction	SNOMED	FALSE	FALSE
4296653	Acute ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery	SNOMED	FALSE	FALSE
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery	SNOMED	FALSE	FALSE
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
761736	Acute ST segment elevation myocardial infarction of anteroapical wall	SNOMED	FALSE	FALSE
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall	SNOMED	FALSE	FALSE

45766116	Acute ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
46274044	Acute ST segment elevation myocardial infarction of lateral wall	SNOMED	FALSE	FALSE
46270161	Acute ST segment elevation myocardial infarction of posterior wall	SNOMED	FALSE	FALSE
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
46270158	Acute ST segment elevation myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
46270164	Acute ST segment elevation myocardial infarction of septum	SNOMED	FALSE	FALSE
45766075	Acute anterior ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
4178129	Acute anteroapical myocardial infarction	SNOMED	FALSE	FALSE
4267568	Acute anteroseptal myocardial infarction	SNOMED	FALSE	FALSE
312327	Acute myocardial infarction	SNOMED	FALSE	FALSE
44782769	Acute myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
44782712	Acute myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
45766115	Acute myocardial infarction during procedure	SNOMED	FALSE	FALSE
434376	Acute myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45766150	Acute myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
438438	Acute myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
4243372	Acute myocardial infarction of apical-lateral wall	SNOMED	FALSE	FALSE
4108669	Acute myocardial infarction of atrium	SNOMED	FALSE	FALSE
4151046	Acute myocardial infarction of basal-lateral wall	SNOMED	FALSE	FALSE
4275436	Acute myocardial infarction of high lateral wall	SNOMED	FALSE	FALSE
438170	Acute myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45771322	Acute myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
438447	Acute myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
441579	Acute myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
436706	Acute myocardial infarction of lateral wall	SNOMED	FALSE	FALSE

4324413	Acute myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
4051874	Acute myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
4303359	Acute myocardial infarction of septum	SNOMED	FALSE	FALSE
4147223	Acute myocardial infarction with rupture of ventricle	SNOMED	FALSE	FALSE
4145721	Acute non-Q wave infarction	SNOMED	FALSE	FALSE
4119944	Acute non-Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119456	Acute non-Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE
4119945	Acute non-Q wave infarction - inferior	SNOMED	FALSE	FALSE
4119946	Acute non-Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4121466	Acute non-Q wave infarction - lateral	SNOMED	FALSE	FALSE
4124685	Acute non-Q wave infarction - widespread	SNOMED	FALSE	FALSE
4270024	Acute non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
35610091	Acute nontransmural myocardial infarction	SNOMED	FALSE	FALSE
319039	Acute posterior myocardial infarction	SNOMED	FALSE	FALSE
444406	Acute subendocardial infarction	SNOMED	FALSE	FALSE
35610093	Acute transmural myocardial infarction	SNOMED	FALSE	FALSE
4119947	Acute widespread myocardial infarction	SNOMED	FALSE	FALSE
37109912	Arrhythmia due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
438172	Atrial septal defect due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124687	Cardiac rupture due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4215259	First myocardial infarction	SNOMED	FALSE	FALSE
4108678	Hemopericardium due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4173632	Microinfarct of heart	SNOMED	FALSE	FALSE
45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture	SNOMED	FALSE	FALSE
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture	SNOMED	FALSE	FALSE

45766212	Mitral valve regurgitation due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4323202	Mixed myocardial ischemia and infarction	SNOMED	FALSE	FALSE
4329847	Myocardial infarction	SNOMED	FALSE	FALSE
37309626	Myocardial infarction due to demand ischemia	SNOMED	FALSE	FALSE
4170094	Myocardial infarction in recovery phase	SNOMED	FALSE	FALSE
4200113	Non-Q wave myocardial infarction	SNOMED	FALSE	FALSE
4030582	Postoperative myocardial infarction	SNOMED	FALSE	FALSE
35610087	Postoperative nontransmural myocardial infarction	SNOMED	FALSE	FALSE
4206867	Postoperative subendocardial myocardial infarction	SNOMED	FALSE	FALSE
35610089	Postoperative transmural myocardial infarction	SNOMED	FALSE	FALSE
4207921	Postoperative transmural myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4209541	Postoperative transmural myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4108679	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction	SNOMED	FALSE	FALSE
4108219	Rupture of chordae tendinae due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124686	Silent myocardial infarction	SNOMED	FALSE	FALSE
765132	Subendocardial myocardial infarction	SNOMED	FALSE	FALSE
45766114	Subsequent ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
45766113	Subsequent ST segment elevation myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45773170	Subsequent ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
4108217	Subsequent myocardial infarction	SNOMED	FALSE	FALSE
4108677	Subsequent myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4108218	Subsequent myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766241	Subsequent non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction	SNOMED	FALSE	FALSE

439693	True posterior myocardial infarction	SNOMED	FALSE	FALSE
37109910	Ventricular aneurysm due to and following acute myocardial infarction	SNOMED	FALSE	FALSE

A4.8. Other arterial thromboembolism

- Intestinal infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4195665	Gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148299	Ischemic colitis	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4319280	Acute bowel infarction	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
44811741	Acute ischaemia of large intestine	SNOMED	FALSE	FALSE
44811740	Acute ischaemia of small intestine	SNOMED	FALSE	FALSE
37117790	Insufficiency of mesenteric artery	SNOMED	FALSE	FALSE
37016198	Epiploic appendagitis	SNOMED	FALSE	FALSE
35622081	Nongangrenous ischemic colitis	SNOMED	FALSE	FALSE
35622080	Gangrenous ischemic colitis	SNOMED	FALSE	FALSE
4345926	Abdominal angina	SNOMED	FALSE	FALSE
4342767	Transient ischemic colitis	SNOMED	FALSE	FALSE
4341648	Hemorrhagic infarction of intestine	SNOMED	FALSE	FALSE
4341646	Occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340939	Non-occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340378	Transmural infarction of intestine	SNOMED	FALSE	FALSE
4340375	Focal segmental ischemia of small intestine	SNOMED	FALSE	FALSE
4318537	Large bowel gangrene	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE

4240850	Acute ischemic enterocolitis	SNOMED	FALSE	FALSE
4239942	Embolic mesenteric infarction	SNOMED	FALSE	FALSE
4237654	Ischemic enterocolitis	SNOMED	FALSE	FALSE
4215949	Nonocclusive intestinal infarction	SNOMED	FALSE	FALSE
4214720	Thrombotic mesenteric infarction	SNOMED	FALSE	FALSE
4192856	Acute ischemic colitis	SNOMED	FALSE	FALSE
4188336	Chronic ischemic enterocolitis	SNOMED	FALSE	FALSE
4174014	Inferior mesenteric artery embolus	SNOMED	FALSE	FALSE
4149013	Mesenteric infarction	SNOMED	FALSE	FALSE
4148257	Chronic gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148256	Acute GIT vascular insufficiency	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055025	Superior mesenteric artery embolus	SNOMED	FALSE	FALSE
4045408	Ischemic stricture of intestine	SNOMED	FALSE	FALSE
201894	Acute vascular insufficiency of intestine	SNOMED	FALSE	FALSE
192673	Vascular insufficiency of intestine	SNOMED	FALSE	FALSE

A4.9. Medications of interest

Concept ID	Code	Concept Name	Domain	Vocabulary
21603933	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	Drug	ATC
21601386	L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Drug	ATC
21600961	B01A	ANTITHROMBOTIC AGENTS	Drug	ATC
21602722	H02	CORTICOSTEROIDS FOR SYSTEMIC USE	Drug	ATC
21603991	M01AH	Coxibs	Drug	ATC
21602472	G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	Drug	ATC
21601853	C10	LIPID MODIFYING AGENTS	Drug	ATC
21602471	G03	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	Drug	ATC
21603831	L02BA01	tamoxifen; oral	Drug	ATC

Annex 5. Preliminary list of negative control outcomes

- *Negative outcome Concept ID*

Concept Id	Outcome Name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary

Concept Id	Outcome Name
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon

Concept Id	Outcome Name
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud’s disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor’s bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets