The comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: an international network cohort study from five European countries and the US

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**Keywords:** COVID-19, Thromboembolism
The comparative association of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: an international network cohort study from five European countries and the US

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SUMMARY BOX

What is already known on this topic

- Thrombosis with thrombocytopenia syndrome (TTS) is being investigated as an adverse reaction of adenovirus-based COVID-19 vaccines.
- The comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events following vaccination with different COVID-19 vaccines remains unclear.

What this study adds

- This is the first multinational analysis of comparative safety of COVID-19 vaccines.
- Using routinely collected data from 5 European countries and the US, we found a 30% increased risk of thrombocytopenia after first-dose ChAdOx1 versus first-dose BNT162b2 vaccination.
- In addition, we found a potential double risk of TTS-VTE with Ad26.COV2.S versus first-dose BNT162b2 vaccine recipients.
- Increased risk of arterial thromboembolism was also seen after single-dose Ad26.COV2.S versus BNT162b2 and versus mRNA-1273 in people aged 20-29 years old.
ABSTRACT (309)

Objective: To quantify the comparative risk of thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events (TE) associated with vaccination with adenovirus-based vs mRNA-based covid-19 vaccines.

Design: International network cohort study.

Setting: Routinely collected health data from France, Germany, the Netherlands, Spain, the UK, and the US.

Participants: Adults registered in any of the contributing databases and exposed to at least one dose of a covid-19 vaccine (ChAdOx1, BNT162b2, mRNA-1273, or Ad26.COV2.S) from December 2020 until the latest data release available in each of the contributing databases.

Main outcome measures: Outcomes were incidence of thrombosis with thrombocytopenia syndrome or thromboembolic events following the 28 days after covid-19 vaccination. Incidence rate ratios (IRR) were estimated after propensity score (PS) matching up to 1:4 adenovirus- vs mRNA-based vaccinated people, and calibrated using negative control outcomes. Database-specific estimates were pooled using random effects meta-analyses.

Results: Overall, 1,332,719/3,829,822 (34.8%) ChAdOx1 recipients were PS matched to 2,124,339/2,149,679 (98.8%) BNT162b2 vaccinees from Germany and the UK. Additionally, we matched 762,517/772,678 (98.7%) people receiving Ad26.COV2.S to 2,851,976/7,606,693 (37.5%) receiving BNT162b2 in Germany, Spain, and the US; and all 628,164 (100%) Ad26.COV2.S recipients from the US to 2,230,157/3,923,371 (56.8%) mRNA-1273 vaccinees. Comparing ChAdOx1 to first-dose BNT162b2, we observed an increased risk of thrombocytopenia (pooled calibrated IRR 1.33 [1.18-1.50]) and a borderline increased risk of TTS in UK data (calibrated IRR 1.29 [0.94-1.77]). Risk of TTS-VTE was borderline increased in Ad26.COV2.S vs 1-dose BNT162b2 vaccines: calibrated IRR 2.26 [0.93-5.52].

Conclusions: In this multinational study of the comparative safety of adenovirus- vs mRNA-based covid vaccines, we observed a 30% increased risk of thrombocytopenia and (borderline) TTS after first-dose ChAdOx1, and a potential double risk of TTS-VTE after a single-dose Ad26.COV2.S versus first-dose mRNA vaccination. Although rare, the observed increase in risk of thrombosis and thrombocytopenia following adenovirus-based vaccines should be considered when planning further immunisation campaigns and future vaccine development.
INTRODUCTION

By May 2021, four COVID-19 vaccines had been granted conditional marketing authorisation by the European Medicines Agency (EMA) after showing high efficacy and safety in phase-3 clinical trials [1–3]. ChAdOx1 (manufactured by AstraZeneca) and COVID-19 Vaccine Ad26.COV2.S are both viral vector-based vaccines. BNT162b2 (manufactured by BioNTech) and mRNA-1273 (manufactured by Moderna) are both mRNA vaccines. After millions of vaccine doses were administered in large-scale immunisation campaigns, rare cases of thrombosis with thrombocytopenia syndrome (TTS) were reported, often after the first dose of viral vector-based vaccines [4–6]. Although fewer concerns have been raised about the safety of mRNA vaccines, instances of immune thrombocytopenia have also been observed in recipients of BNT162b2 [7].

A causal relationship was considered by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), leading to an update of the product information to include TTS as a very rare side effect [8]. As these unusual blood clots in combination with thrombocytopenia were reported predominantly in women younger than 60 years, several European countries restricted the use of viral vector-based vaccines in younger age groups as a precautionary measure. While the pathogenesis is not yet fully understood, an immune response leading to the development of pathologic platelet-activating antibodies has been suggested and named vaccine-induced immune thrombocytopenia (VITT) [6,9]. Although these events are very rare, absolute numbers of affected patients may become substantial due to the large numbers of vaccine doses administered worldwide.

Although some observational studies have examined the risk of TTS events after COVID-19 vaccination in some European countries [10–13], there is no clear evidence on the comparative safety profile of different vaccines. Given the high number of SARS-CoV-2 infections and reinfections seen worldwide, and the known impact of COVID-19 vaccines to minimise severity and complications, it is essential to understand the risks of the available vaccines compared to each other, rather than comparing them to no vaccination. We therefore aimed to quantify the comparative risk of TTS or thromboembolic events (TE) associated with vaccination with adenovirus-based versus mRNA-based COVID-19 vaccines.
METHODS

Study design: We conducted an international network cohort study using routinely collected health care data mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The OMOP CDM allowed the study to be run by each site with common analytic code. Results were aggregated without sharing patient-level data.[14–16]

Data sources: Datasets from five European countries (France, Germany, Netherlands, Spain, and the United Kingdom) and two datasets from the United States informed the analyses. IQVIA Longitudinal Patient Data (LPD) France is a centralized anonymized patient electronic medical records database contributed by general practices (GPs).[17] IQVIA Disease Analyser (DA) Germany is collected from extracts of patient management software used by general medicine and specialists practicing in ambulatory care settings. The Integrated Primary Care Information (IPCI) database is a Netherlands-based electronic healthcare records data collected from patients registered with GPs[18]. The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximately 80% of the population of Catalonia, Spain. SIDIAP was linked to the regional vaccination registry and to hospital discharge data (CMBD-HA) for this study.[19] The Clinical Practice Research Datalink (CPRD) AURUM database collects anonymized primary care electronic health records from GPs across the UK, which are linked at origin to national vaccination records.[20] The IQVIA hospital charge data master (IQVIA Hospital CDM) dataset comprises records from hospital charge data master files from the US and records both inpatient and outpatient encounters.[21] The US Open Claims dataset includes medical claims covering approximately 191 million patients across the US, with patient-level office visit, outpatient, and inpatient information (Table 1).

The study period to identify exposures and outcomes covered from December 2020 (first vaccines administered) until the latest data release available in each of the contributing databases.

Study participants: The study population were adults (aged 18 or over at vaccination date) registered in any of the contributing databases and exposed to at least one dose of a brand-specific covid-19 vaccine during the study period. We required a minimum of 1 year of history available in the database before index vaccination date. We excluded individuals who did not have a vaccine brand specified (unspecific vaccine codes) during the study period. We also excluded people who received their second dose within 14 days after the first dose, as these were likely errors in vaccination records. We included only people with complete age and sex recorded.

Four brands of covid-19 vaccines were included: ChAdOx1, BNT162b2, mRNA-1273, and covid-19 Vaccine Ad26.COV2.S. Vaccines were identified by procedure, drug, or observation codes in each database (Supplementary data B). We built first- and second-dose cohorts for each brand. In the second dose cohorts, we didn’t include individuals whose second dose vaccine brand was different from their first dose. A single-dose cohort was built for covid-19 Vaccine Ad26.COV2.S as it was approved for a single-dose schedule at the time of protocol approval. Comparisons were made between the adenovirus-based vaccines (ChAdOx1 or covid-19 Vaccine Ad26.COV2.S, the “target”) and mRNA vaccines (BNT162b2 or mRNA-1273, the “comparator”).

The index date for the first-dose vaccination cohorts was defined as the date of the first covid-19 vaccination for a specific brand. The index date for the second-dose vaccination cohorts was
defined as the date of the second covid-19 vaccination. We followed individuals from their index
date to 28 days after vaccination, death, or loss of visibility in the database (e.g., person leaving
the practice in electronic health records data, or end of continuous enrolment in claims data),
whichever comes first. The 28 days risk window is based on the definition from WHO and UK
MHRA guidelines.[22,23]

Due to computing expense, we used a random sample of 20% of each cohort when using US Open
claims data.

**Primary outcomes:** The primary outcomes were thromboembolic events and thrombosis with
thrombocytopenia syndrome (TTS).

Thromboembolic events of interest included: deep-vein thrombosis, pulmonary embolism, venous
thrombo-embolism as a composite of deep-vein thrombosis or pulmonary embolism, cerebral
venous sinus thrombosis (CVST), splanchnic and visceral vein thrombosis (SVT), ischemic stroke,
myocardial infarction, and arterial thromboembolism as a composite of ischemic stroke,
myocardial infarction, and other rare arterial thromboembolisms, such as intestinal
infarction, defined in Supplementary Materials B.

The definition of TTS (Supplementary data B) was based on that proposed by the Brighton
Collaboration and encompassed the occurrence of any thromboembolic event of interest with
concurrent thrombocytopenia within 10 days before or after a thromboembolic event occurring
after vaccination. Thrombocytopenia was identified by a diagnostic code or measurement of
<150,000 platelets per microliter of blood, as proposed by the Brighton collaboration[24]. This
definition has been used in previous OMOP CDM-based studies.[25]

We used two alternative TTS definitions in sensitivity analyses: 1. Requiring the concurrent
thrombocytopenia happened within 5 days before of after the thromboembolic event after
vaccination. 2. Reducing the threshold to <100,000 platelets per microliter for the definition of
thrombocytopenia based on laboratory data.

**Negative control outcomes:** Negative controls are outcomes that are not expected to be causally
associated with the exposure, which is vaccination. We used 92 negative control outcomes
previously used for vaccine safety[26]. They were pre-specified based on clinical knowledge and
previous literature, validated by two clinicians, and tested in previous work on other vaccine
safety projects[27]. Supplementary materials A, Table 1 shows the codes for these negative
control outcomes.

**Covariates:** We defined baseline patient characteristics as potential confounders based on
information recorded before index date, including: demographics (age, sex, index year, and index
month); clinical condition at any time before cohort index; composite comorbidity (Charlson Index-
Romano adaptation[28]) and thrombosis score (CHA2DS2-VASc, congestive heart failure
hypertension – vascular disease[29]); records and total number of medicines, procedures, and
measurement records observed in the 6 months before cohort index.
Statistical analysis: Descriptive statistics were used to report the baseline characteristics for each cohort. We reported the 28-day database-specific incidence rate and corresponding 95% confidence intervals for each event.

We used propensity-score matching to minimise observed confounding. We calculated propensity scores for each pair of comparisons (target and comparator) using large-scale L1 regularized logistic regression[30], which included all available baseline patient characteristics in the databases. A simulation study by Tian et al[31] found that this approach was preferable to a traditional propensity score calculated with a predefined set of covariates defined by experts. The derived propensity score was used to match patients using greedy matching with a caliper width of 0.2 standard deviation of the logit at a ratio of up to 1 to 4. If the target cohort is larger than the comparator cohort, reverse matching is allowed where 4 to 1 ratio will be used.

We used three diagnostics to evaluate measured confounding, statistical power, and unmeasured confounding. We did not complete any analysis that failed the measured confounding and statistical power diagnostics to avoid biased estimates. First, the control for measured confounding, only target-comparator vaccine pairs with all covariates showing a standardized mean difference (SMD) lower than 0.1 after propensity-score matching were considered satisfactory. Second, we calculated the minimum detectable rate ratio (MDRR) using α of 0.05 and power of 80% for each outcome of interest in both the crude and propensity score matched cohorts[32]. No estimates of incidence rate ratios were reported where the MDRR for a database-target-comparator outcome combination was >5, as this was deemed too underpowered and therefore unreliable. Third, we used associations with negative control outcomes to assess residual confounding. We pre-specified that <20% negative control outcomes should be associated with vaccination exposure. Results for those that failed the unmeasured confounding diagnostic are reported, but only empirically calibrated estimates should be relied upon.

We used Poisson regression to calculate the incidence rate ratio (IRR) and 95% confidence intervals of outcomes according to the target and comparator vaccinations. Following reviewers’ suggestions, we also estimated incidence rate difference and 28-day absolute risk differences for associations with a significant calibrated IRR.

We used empirical calibration to account for residual systematic error due to potential unobserved confounding[34,35]. To perform calibration, we first derived an empirical null distribution from the actual effect estimates for the negative control outcomes. We then used the null distribution to compute the calibrated p-value and confidence intervals. This approach has been used in many previous studies in different clinical areas, including covid-19 repurposed therapies[36–38], and was acknowledged in the latest version of the EnCePP guide on methodological standards in pharmacoepidemiology.[39]

Finally, we conducted random effect meta-analysis to pool database-specific results where I² was <40%. Only estimates from database-target-comparator combinations that passed the covariate balance diagnostic were included.

We stratified all analyses by age (10-year bands) and sex as pre-specified per protocol. Only strata with sufficient power (MDRR<5) were reported.

All analyses were pre-specified in a registered study protocol (link), and conducted in R 3.6.0 using the open-source Observational Health Data Science and Informatics (OHDSI) tool-stack, the Cyclops and EvidenceSynthesis packages available via CRAN. All our analytical code is available for review in a dedicated Github repository (link).
RESULTS

We identified 4.0 million people vaccinated with a first dose of ChAdOx1 (3,789,631 in UK CPRD, 98,562 in DA Germany, 27,698 in LPD France, and 71,083 in IPCI Netherlands) and 1.6 million people vaccinated with a second dose (1,195,626 in UK CPRD, 307,344 in SIDIAP Spain, 31,200 in Germany DA data, 15,067 in LPD France, and 38,884 in IPCI Netherlands) from all participating databases. We identified 1.1 million people vaccinated with single-dose Ad26.COV2.S covid-19 vaccine in three databases (37,723 in DA Germany, 138,351 in SIDIAP Spain, and 939,748 in US OpenClaims). We identified 10.6 million people vaccinated with a first dose of BNT162b2 (1,840,240 UK CPRD, 391,063 DA Germany, 281,743 Hospital CDM US, 6,055,337 US OpenClaims, and 2,027,950 SIDIAP Spain), and 7.7 million people vaccinated with a second dose (1,369,238 CPRD UK, 321,099 DA Germany, 230,036 Hospital CDM US, 4,450,735 US OpenClaims, and 1,357,509 SIDIAP Spain). We identified 4.3 million people vaccinated with a first dose of mRNA-1273 (70,957 US Hospital CDM and 4,260,380 US OpenClaims data), and 3 million people vaccinated with a second dose (58,688 Hospital CDM US, 2,938,023 US OpenClaims). Cohort characteristics are summarized in Supplementary material A, and Tables 2 (European) and 3 (US databases).

Figure 1. Cohort selection, using CPRD Aurum, first-dose ChAdOx1 (target) vs BNT162b2 (comparator) as an example.

First-dose ChAdOx1 (Target): 3,789,631
First-dose Comirnaty (Comparator): 1,840,240

Exclude patients with prior outcome:
Target: 166,970
Comparator: 115,853

Target: 3,622,661
Comparator: 1,724,387

Exclude days at risk less than one:
Target: 763
Comparator: 269

Target: 3,621,898
Comparator: 1,724,118

Not matched on propensity score:
Target: 2,426,400
Comparator: -111,994

Study population:
Target: 1,195,498
Comparator: 1,836,112

Noticeable differences existed in baseline patient characteristics before matching when comparing first-dose ChAdOx1 with first-dose BNT162b2 vaccinees in UK CPRD data (Table 2). BNT162b2 vaccinees were more likely to be female (58.2% vs. 51.5%) and older and had a higher prevalence of comorbidities of interest. They were also more likely to use common medications such as hypertension and diabetes treatments.
To reduce measured confounding, we estimated propensity scores for each vaccine pair and database. Supplementary Table 14 summarizes the top 10 variables with stronger association with vaccine type in each of the databases. Propensity score matching led to a final cohort of 1.2 million ChAdOx1 and 1.9 million vaccinees BNT162b2 vaccinees (Figure 1, Table 2). Post-matching patient characteristics were comparable for most vaccination cohort pairs and databases, and are described in detail in Tables 2-4 and Supplementary materials A, Tables 4-6. The cohort selection process of all included cohorts are detailed in Supplementary table 13.

**Study diagnostics: confounding and statistical power**

We applied three diagnostic tests to evaluate the robustness of our analyses, based on measured confounding, statistical power, and unmeasured confounding. Supplementary materials A, Table 7 summarises the diagnostics. First, to avoid bias due to confounding, we did not analyse cohorts with substantial differences after matching: fourteen analyses passed this diagnostic, where no patient characteristic had a standardized mean difference (SMD) of >=0.1 after propensity score matching. Conversely, no analysis was conducted in the US Hospital CDM, as residual confounding was noted (SMD>0.1 for >=1 variables). Second, eight analyses had sufficient statistical power for at least one outcome, as noted by MDRR <5. Unfortunately, LPD France and US Hospital CDM databases failed the power diagnostics for all study outcomes. Therefore, no database-specific estimates are reported for any of them. Third, negative control outcomes (NCO) were used to identify residual confounding. Of the seven combinations with sufficient NCOs, three had >20% of them associated with vaccine use, suggesting the presence of substantial systematic error (Supplementary materials A, Figures 1 and 2). Most of the estimates for these NCOs had a RR>1, suggesting that our uncalibrated results overestimate risks, and that only calibrated results should be considered adequate. However, too few negative control outcomes were observed in IPCI and DA Germany, precluding calibration.

**Comparative safety**

Crude incidence rates before matching are available in Supplementary materials A, Tables 8 and 9. Database-specific results from the seven combinations that passed diagnostics after matching are reported in Table 5. Comparison between the matched first-dose ChAdOx1 and BNT162b2 cohorts was completed in the UK CPRD Aurum, Germany DA, France LPD, and the Netherlands IPCI. Seven outcomes were estimated in more than one database, and therefore included in meta-analyses. Figure 2 depicts meta-analytic incidence rate ratios (IRRs) for all analyses where 2 or more databases contributed after diagnostics.

We found an increased risk of thrombocytopenia following ChAdOx1 in UK CPRD data, where there were 827 and 442 thrombocytopenia events following first-dose ChAdOx1 and BNT162b2, respectively. Incidence rates (IRs [CIs]) were 6.06 per 1,000 person-years (95% CI: 5.65-6.48) and 4.89 (95% CI: 4.45-5.37) respectively, with calibrated IRR 1.31 (1.16-1.49). This was not replicated in Germany DA data: calibrated IRR: 1.01, 95% CI: 0.63-1.62. Meta-analyses resulted in a pooled calibrated IRR of 1.33 (95% CI: 1.18-1.50) (Figure 2), a calibrated incidence rate difference of 1.18 (95% CI: 0.57 to 1.8) per 1,000 person-years, and an absolute risk difference of 8.21 (95% CI: 3.59 to 12.82) per 100,000 vaccinees. No differential risk of thrombocytopenia was seen after the second dose of ChAdOx1 (vs 2-dose BNT162b2): meta-analytic calibrated IRR 0.93 (0.78-1.11), see Figure 2. Similarly, no increased risk of thrombocytopenia was noted after Ad26.COV2.S vs 1-dose BNT162b2: meta-analytic calibrated IRR 1.08 (0.58-1.99), see Figure 2.

A borderline increase in risk of VTE was seen following 1-dose ChAdOx1 (vs BNT162b2) in Germany DA (calibrated IRR 1.61 (0.92-2.83)), but not replicated in UK CPRD (IRR 0.91 (0.78-
1.06)), see Table 2. Meta-analysis was unreliable due to heterogeneity (I^2 65%). Similarly, an increased risk of deep vein thrombosis was seen following 1-dose ChAdOx1 vs BNT162b2 in DA Germany (calibrated IRR 2.62, 95% CI: 1.34-5.13), but not replicated in UK data (calibrated IRR 0.89 (0.71-1.11)), see Table 2. Again, the meta-analytic estimate was unreliable due to heterogeneity (I^2 86%). No increased risk of pulmonary embolism was seen in either database, with calibrated IRR 0.93 (0.77-1.12) and 0.69 (0.26-1.83) in UK and German data respectively. No differential risks of VTE, DVT or PE were noted when comparing second-dose ChAdOx1 vs BNT162b2 (Table 2, Figure 2). In line with this, no association was seen between vaccination with Ad26.COV2.S and any venous thromboembolic event, in database-specific (Table 2) or pooled meta-analysis (Figure 2). Regarding rare thrombosis, the meta-analysis showed a lower risk of intestinal infarction for the Ad26.COV2.S covid-19 vaccine users vs 1-dose BNT162b2, with pooled calibrated IRR of 0.37 (95% CI: 0.15-0.89), an incidence rate difference of -0.41 (95%CI: -1.17 to 0.35) per 1,000 person-years, and an absolute risk difference of -3.34 (95%CI: -9.77 to 3.09) per 100,000 vaccinations (Figure 2). No other rare thrombotic events had differential risks between cohorts.

For composite arterial thromboembolism, the pooled calibrated IRR for 1-dose ChAdOx1 vs 1-dose BNT162b2 was 0.87 (95% CI: 0.75-1.01) (Figure 2). The two reliable database-specific analyses in Table 2 showed consistent findings: calibrated IRR 0.85 (0.73-0.99) in CPRD UK, and 0.76 (0.41-1.39) in DA Germany. Consistent with this, no differences in risk of ATE, ischemic stroke, or myocardial infarction were seen after second-dose ChAdOx1 (vs 2-dose BNT162b2) or after Ad26.COV2.S vs 1-dose BNT162b2 (see Table 2 and Figure 2). Similar results were seen also for ischemic stroke and myocardial infarction when analysed separately (Table 2, Figure 2).

Thrombosis-thrombocytopenia (TTS) was rare and could only be analysed for ChAdOx1 in UK data. Risk of TTS was borderline increased in CPRD following 1-dose ChAdOx1 vs 1-dose BNT162b2 (calibrated IRR 1.29 (0.94-1.77)), but not clearly after second dose (calibrated IRR 1.16 (0.71-1.89)). As for Ad26.COV2.S vaccine, no differential risk was seen, with US data showing a calibrated IRRs of 1.11 (0.67-1.84) in the comparison against 1-dose BNT162b2 and of 0.97 (0.61-1.55) when compared to 1-dose mRNA-1273 (Table 2). Conversely, a borderline significant association was seen for TTS with VTE: calibrated IRR 2.45 (0.95-6.29) for Ad26.COV2.S vs 1-dose BNT162b2 and 1.92 (0.77-4.80) vs 1-dose mRNA-1273.

Sensitivity and subgroup analyses

Sensitivity analyses restricting the time window for TTS to 5 days or reducing the threshold of platelet count (to lower than 100,000 platelets per microliter) found results consistent with the main analysis (Table 6).

Stratified analyses are reported in Supplementary Tables 11 and 12, and include findings from the UK CPRD and US OpenClaims databases, as these were the only ones with sufficient power (MDRR<5) for at least 1 outcome. An increased risk of thrombocytopenia was observed in the 40 – 49 years old, 70 – 79 years old, and women receiving 1-dose ChAdOx1 vs 1-dose BNT162b2 in the UK data. Additionally, the calibrated IRR for composite arterial thromboembolism following ChAdOx1 vs BNT162b2 was somewhat lower in male, with calibrated IRR 0.75, 95% CI: 0.61-0.92 (Supplementary table 11). Conversely, a subgroup analysis in the OpenClaims US data found an increased risk of ATE following the Ad26.COV2.S covid-19 vaccine in people aged 20-29 years old: calibrated IRR 4.64 (95%CI: 2.16-9.97) and 5.10 (95%CI: 1.71-15.19) for comparison versus BNT162b2 and mRNA-1273 respectively. This was not replicated in any other subgroups.
Figure 2. Meta-analysis estimates of calibrated incidence rate ratios.

Caption: solid line: calibrated; dashed line: uncalibrated; TTS-VTE: Venous thrombo-embolism with thrombocytopenia syndrome; TTS-DVT: Deep vein thrombosis with thrombocytopenia syndrome (TTS-DVT).
DISCUSSION

This is the first multinational analysis of the comparative safety of adenovirus- vs mRNA-based COVID-19 vaccines. In this matched cohort study, we compared the rates of thrombosis and thrombocytopenia within 28 days after vaccination. We used routinely collected health data from five European countries and the USA, and produced risk estimates after applying state-of-the-art methods to minimize confounding and systematic error. We observed a 30% increased risk of thrombocytopenia and a similar albeit borderline excess risk of TTS after first-dose ChAdOx1 versus first-dose BNT162b2. We also identified a borderline double risk of TTS-VTE after 1-dose Ad26.COV2.S versus BNT162b2. Our international analysis allowed us to analyse both adenovirus-based vaccines to confirm TTS as a potential class effect.

Subgroup analyses showed potential a 25% lower risk of ATE following 1-dose ChAdOx1 (vs BNT162b2) in UK-based men, and a 4 to 5-fold increased risk of ATE in younger people (age 20-29) vaccinated with Ad26.COV2.S vs either mRNA vaccine in the US. However, these findings were not replicated in other data sources or in other age strata.

TTS, or vaccine-induced immune thrombotic thrombocytopenia (VITT), was first reported after the administration of the ChAdOx1 vaccine in early 2021[4,5]. A disproportionality analysis using the World Health Organization’s VigiBase database reported a safety signal for CVST and ischemic stroke for ChAdOx1, BNT162b2, and mRNA-1273 [40]. The authors called for well-designed comparative safety studies on adverse events of all three vaccines. A study based on Danish and Norwegian data also found higher-than-expected rates of VTE, pulmonary embolism, and CVST after vaccination compared to background rates [10]. While these studies provided important insights into the incidence of adverse outcomes reported after vaccination, they failed to adjust for potential confounders including comorbidity, frailty, nursing home residence, or history of other risk factors for thrombosis or coagulopathy.

The risk of post-vaccination thrombocytopenia has been studied by comparing vaccinated with unvaccinated groups, and using self-controlled designs. Hippisley-Cox et al. conducted a self-controlled case series analysis of English data including approximately 30 million vaccinated people[12]. They provided epidemiological evidence of a 30% increased risk of thrombocytopenia and venous thromboembolism after ChAdOx1, and an elevated risk of CVST after ChAdOx1 and BNT162b2. In a population-based cohort study in England, Whiteley et al reported increased rates of thrombocytopenia during the 1 to 28 days after ChAdOx1 compared to unvaccinated people among those aged below 70, but no association with BNT162b2. [42] Our study is the first to compare both vaccines, and found a 30% excess risk of thrombocytopenia after ChAdOx1 compared with BNT162b2, consistent with previous studies.

Regarding ATE, a study from Scotland found an increased risk of arterial thromboembolic events in nested case-control analyses, which was attenuated in self-controlled case series analyses.[13] An English self-controlled case series study found an increased risk of ATE after BNT162b2 but not ChAdOx1 [12]. Whiteley et.al reported lower rates of major ATE and VTE after vaccination with both ChAdOx1 and BNT162b2 compared to unvaccinated people, after adjusting for potential confounding factors.[42] Partially consistent with these, we observed a lower rate of ATE after ChAdOx1 compared with BNT162b2 in UK CPRD data, not replicated elsewhere or with other adenovirus-based vaccines (Ad26.COV2.S vs BNT162b2). Our finding of an increased risk of ATE in young people after Ad26.COV2.S vaccine (vs mRNA vaccines) in US data did not replicate elsewhere or with ChAdOx1, and needs further research.
Some of our study outcomes, such as CVST, SVT, and TTS, were very rare. Kerr et al reported that CVST was observed approximately 16.34 per million doses of ChAdOx1, and 12.60 per million doses of BNT162b2. In a previous self-controlled case series analysis using data from England, Scotland and Wales, ChAdOx1 was associated with an elevated risk of CVST in the 28 days following ChAdOx1, IRR = 1.93 (95% CI 1.20 to 3.11) but not after BNT162b2. [11] Similarly, a large record linkage study of hospital admissions in England showed an increased risk of CVST after first-dose ChAdOx1, seen only in adults younger than 65 years old, and not after BNT162b2.[43] A US case series using the Vaccine Adverse Event Reporting System estimated rates of TTS were 3.83 per million vaccine doses of the Ad26.COV2.S covid-19 vaccine and 0.00855 per million vaccine doses of mRNA-based covid-19 vaccines[44]. Yet the authors stated that TTS cases reported after mRNA vaccines are among different demographic characteristics and medical history compared to cases after the Ad26.COV2.S vaccine. Passive surveillance tends to suffer from underreporting. In comparison, we used routinely collected health data and were able to estimate the comparative risks between vaccines, therefore minimising surveillance bias. In a previous study, we reported that background incidence rates varied across data sources, and suggested within-database analyses for historical rate comparisons[45]. In the present study, while we didn’t see huge heterogeneity of post vaccine incidence rates between databases, relative rates varied. In our meta-analysis, the pooled estimates were largely driven by databases with larger sample size such as the CPRD UK and OpenClaims US data.

**Strengths and Limitations**

The results of our study should be interpreted in the context of its known limitations. Due to heterogeneity across data sources, misclassification of vaccine exposures and outcomes may be problematic. Regarding vaccine exposure, the UK and Spanish data sources captured vaccine information more reliably than previous studies through linkage to official vaccination registries. In contrast, the German and French records and US datasets are expected to include incomplete vaccine records. The use of comparative safety analyses minimises the impact of this problem, as only vaccinated cohorts are included for analysis.

Information bias due to outcome ascertainment is likely to be present in our study. We used robust methods for the creation and transportation of algorithms for the identification of all of the study events [25]. However, some study events typically treated in hospital could be incompletely captured in some of our databases, including the German and French data sources. Fortunately, inpatient data was available for the Spanish database through linkage and for US claims based on reimbursement. Our choice of matched cohort design should additionally minimise the impact of misclassification, as we do not expect incompleteness to be conditional on the vaccine received.

Each country has its own immunization schedule, and the studied vaccines were not all approved at the same time. For example, the vaccination campaign began on 8 December 2020 in England, and BNT162b2 were firstly given to care home residents, people aged ≥80 years, and frontline health workers, followed by vulnerable and people aged ≥70 years. Individuals vaccinated earlier therefore have higher background rates especially for thromboembolic events. Age and calendar time were therefore essential confounders, accounted for in our propensity score models. Propensity score matching created comparable cohorts, at the cost of excluding those with extreme propensity score values, who could not find a match. For example, in the UK CPRD, while 11% of the original BNT162b2 cohort was indexed in December 2020, almost all were excluded after matching. This should be taken into account when interpreting our findings.
As we analysed data up to mid-2021, only the first and second waves of the pandemic were represented. However, the proportion of included people with a history of covid-19 infection before vaccination was balanced in all eligible comparisons, both before and after matching.

In our study, we reported the database-specific incidence rates of outcomes for both the original full cohorts and the propensity score matched cohorts. The incidence rates from the full cohorts were crude without any adjustment. While reflecting the real-world incidence, they were highly subjected to the population characteristics and thus were not directly comparable between cohorts. The incidence rates from matched cohorts, on the other hand, can be compared since the propensity score matching accounted for the measured confounding. Caution is needed when interpreting these incidence rates as the generalizability of the rates is limited.

Our study also has important strengths. While other epidemiological methods have been used in vaccine safety studies, a cohort study with active comparators enabled us to directly estimate the relative risk of developing thromboembolic events or TTS after different covid-19 vaccines, which is not feasible in self-controlled designs or observed-to-expected analyses. Our study therefore answers a more reliable question at this stage of the pandemic (“what vaccine is safer?” instead of “are vaccines safer than no vaccination?”). The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) allowed us to replicate the exact same analysis across different databases, therefore improving robustness, transparency, and reproducibility.

To reduce bias and confounding and ensure the reported results are reliable, we used robust diagnostics in our study design and statistical analysis plan. We used large-scale propensity score modelling based on an L1 regularized logistic regression to minimise observed confounding. This approach has been shown to preferable to traditional PS estimation [31]. We examined residual confounding after matching, and did not perform analyses where relevant confounding was observed. Further, we leveraged previously validated negative control outcomes [27,46] to assess risk of residual (unobserved) bias. Empirical calibration was then used to minimize any remaining systematic error.

**Conclusions**

In conclusion, we identified a 30% increase in the risk of developing thrombocytopenia and a similarly sized (although borderline significant) excess risk of TTS with first-dose ChAdOx1 versus BNT162b2. Our findings also suggest a borderline significant increased risk of TTS-VTE following vaccination with Ad26.COV2.S covid-19 compared to first-dose BNT162b2. These findings should be considered to inform further vaccination campaigns and for the monitoring of any future adenovirus-based vaccines in pipeline.
FOOTNOTES

Data availability statement: Patient level data cannot be shared without approval from data custodians owing to local information governance and data protection regulations. The analytic code is available at: https://github.com/oxford-pharmacoepi/ROC22_CovVaxComparativeSafety/tree/main/CovVaxComparativeSafety. Additional correspondence and requests for materials should be addressed to the corresponding author (EB).

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Contributors: Xintong Li, Victoria Strauss, and Daniel Prieto-Alhambra designed the study, and Katia Verhamme and Catherine Cohet reviewed and approved the study protocol. XL, VS, DPA wrote the related analysis plan, and KV and CC reviewed and approved it. Talita DS, Can Y, C Reich, A Delmestri, P Rijnbeek, M Mosseveld, Luis H John, MA Mayer, JM Ramirez-Anguita, E Burn and X Li curated and/or analysed the data. Marc Suchard and Kelly Li contributed to analytical coding and related software. DPA, KV, and PR were responsible for funding application/s and project management. XL and DPA wrote the first draft of the current manuscript, and all co-authors provided feedback and approved the final version for submission.

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Competing interests: DP-A receives funding from the UK National Institute for Health Research (NIHR) in the form of a senior research fellowship and from the Oxford NIHR Biomedical Research Centre. XL receives the Clarendon Fund and Brasenose College scholarship (University of Oxford) to support her DPhil study. DP-A’s research group has received research grants from the European Medicines Agency; the Innovative Medicines Initiative; and Amgen, Chiesi, and UCB Biopharma; and consultancy or speaker fees from Astellas, Amgen, AstraZeneca, and UCB Biopharma. LHJ works for a research group who received/receives unconditional research grants from Yamanouchi, Pfizer-Boehringer Ingelheim, Novartis, GSK, Chiesi, Astra-Zeneca, Amgen, Ad26.COV2.S Research & Development. None of which relate to the content of this paper. PR works for a research group who received/receives unconditional research grants from Yamanouchi, Pfizer-Boehringer Ingelheim, Novartis, GSK, Chiesi, Astra-Zeneca, Amgen, Ad26.COV2.S Research & Development. None of which relate to the content of this paper.

The lead authors (XL) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We will disseminate a lay summary of our findings through our Twitter and other social media accounts.
Patient and Public Involvement: Owing to the nature of this study and data privacy constraints, no patients or members of the public were involved in the study design, analysis, interpretation of data, or revision of the manuscript.

Ethics approval: The protocol for this research was approved by the independent scientific advisory committee for Medicine and Healthcare Products Regulatory Agency database research (protocol No 21_000641). Informed consent of individual patients was not required as anonymised information was obtained from medical records.
REFERENCES


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Table 6. Sensitivity analysis: Incidence rates (IR per 1,000 py) and IRR for adenovirus vs mRNA-based vaccination in analyses that passed diagnostics.
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904x387mm (118 x 118 DPI)
Tables of “The comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: an international network cohort study from five European countries and the US”

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Table 1. Database descriptions

<table>
<thead>
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<th>Key data available</th>
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Table 2. Baseline characteristics of eligible ChAdOx1 cohorts of vaccinated people identified EU based databases.

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<tr>
<td>Malignant tumor of colon</td>
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<tr>
<td>Malignant tumor of lung</td>
<td>0.2 0.3 0.00 0.3 0.3 0.00 0.2 0.3 0.00 0.2 0.3</td>
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<table>
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<tr>
<td>Antithrombotic agents</td>
<td>4.4 8.9 0.00 7.8 7.7 0.00 14.1 14.2 0.00 14.9 15.5</td>
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<tr>
<td>Drugs for acid related disorders</td>
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<td>Calcium channel blockers</td>
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</tr>
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</tr>
<tr>
<td>Drugs for obstructive airway diseases</td>
<td>9.5 11.9 0.00 12.1 12.1 0.01 11.4 10.4 0.03 12.1 12.5</td>
</tr>
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<tr>
<td>Antiepileptics</td>
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<td>Psychotropic</td>
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<td>Antipsychotics</td>
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Table 3. Baseline characteristics of eligible Janssen COVID-19 cohorts of vaccinated people identified EU based databases.

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<tr>
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<th>SIDIAP Before PS matching</th>
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<td>Janssen</td>
<td>Janssen</td>
<td>Janssen</td>
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<td>21</td>
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<tr>
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<td>Atrial fibrillation</td>
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<td></td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Heart disease</td>
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<tr>
<td>Heart failure</td>
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<td></td>
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<tr>
<td>Peripheral vascular disease</td>
<td>4.1 5.8 -0.08 6.9 7 0.00 1.7 2.5 -0.06 1.7 1.7 -0.01</td>
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<tr>
<td>Pulmonary embolism</td>
<td>0.6 1.5 -0.09 0.8 0.8 0.00 0.4 0.7 -0.04 0.4 0.4 0.00</td>
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<tr>
<td>Venous thrombosis</td>
<td>4.2 5.7 -0.07 4.3 4.3 0.00 2.9 3.8 -0.05 2.9 2.8 0.00</td>
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<table>
<thead>
<tr>
<th>Medical history: Neoplasms</th>
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<tr>
<td>Malignant tumor of breast</td>
<td>0.9 2.3 -0.12 1.2 1.1 0.01 1.2 1.8 -0.05 1.3 1.3 0.00</td>
</tr>
<tr>
<td>Hematologic neoplasm</td>
<td>0.6 1.2 -0.04 1.1 1.1 0.00 0.6 1 -0.04 0.6 0.7 -0.01</td>
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<tr>
<td>Malignant lymphoma</td>
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</tr>
<tr>
<td>Malignant neoplasm of anorectum</td>
<td>0.2 0.4 -0.04 0.3 0.3 0.00 0.2 0.4 -0.03 0.3 0.3 0.00</td>
</tr>
<tr>
<td>Malignant neoplastic disease</td>
<td>7.1 12.8 -0.19 10 10 0.00 7.1 11.9 -0.16 7.5 7.4 0.00</td>
</tr>
<tr>
<td>Malignant tumor of lung</td>
<td>0.1 0.3 -0.05 0.2 0.2 -0.01 0.2 0.2 -0.02 0.2 0.2 0.00</td>
</tr>
<tr>
<td>Malignant tumor of urinary bladder</td>
<td>0.2 0.4 -0.04 0.3 0.3 0.00 0.5 0.9 -0.05 0.6 0.6 0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication use</th>
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<tr>
<td>Lipid modifying agents</td>
<td>10.9 17.1 -0.16 20.3 20.4 0.00 15.3 19.6 -0.11 15.5 15.4 0.00</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>8.1 14.2 -0.20 14.7 14.9 -0.01 9.6 16.3 -0.20 9.7 9.7 0.00</td>
</tr>
<tr>
<td>Agents acting on the renin-angiotensin system</td>
<td>23 30.6 -0.17 42.4 42.6 0.00 18.9 25.7 -0.17 18 18 0.01</td>
</tr>
<tr>
<td>Diuretics</td>
<td>11.5 17.2 -0.16 21.4 21.5 0.00 12 18.9 -0.19 12 12 0.01</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>10.1 13.7 -0.11 18.9 19 0.00 6 9.2 -0.12 6.1 5.9 0.01</td>
</tr>
<tr>
<td>Antinflammatory and antirheumatic products</td>
<td>17.6 19 -0.03 28.6 27.1 -0.01 23.9 24.1 0.00 23.9 24.1 0.00</td>
</tr>
<tr>
<td>Drugs used in diabetes</td>
<td>7.5 10.4 -0.10 13.8 13.8 0.00 9 10.7 -0.06 8.9 8.9 0.00</td>
</tr>
<tr>
<td>Drugs for obstructive airway diseases</td>
<td>7.3 10.2 -0.10 11.4 11.5 0.00 12.6 14 -0.04 12.7 12.7 0.00</td>
</tr>
<tr>
<td>Antibacterials for systemic use</td>
<td>6.3 7.9 -0.06 8.6 8.8 -0.01 13.6 14.6 -0.03 13.5 13.7 0.00</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>0.5 1 -0.05 0.9 0.9 0.00 0.7 1 -0.04 0.7 0.6 -0.01</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>0.4 1 -0.05 0.6 0.6 0.00 0.6 1 -0.04 0.7 0.6 -0.01</td>
</tr>
<tr>
<td>Antiepileptics</td>
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</tr>
<tr>
<td>Psycholeptics</td>
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<td>Psychostimulants, agents used for adhd and nootropics</td>
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</tr>
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</table>
Table 4. Baseline characteristics of eligible Janssen COVID-19 cohorts of vaccinated people identified US database.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before PS matching</th>
<th>After PS matching</th>
<th>Before PS matching</th>
<th>After PS matching</th>
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<td>16.6</td>
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<td>10.4</td>
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<td>-0.05</td>
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<td>Charlson index - Romano adaptation</td>
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<td>Covid-19 infection prior vaccination</td>
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<td>-0.02</td>
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<td>3.8</td>
<td>-0.03</td>
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<td>-0.01</td>
<td>0.6</td>
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<tr>
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<td>-0.01</td>
<td>1.4</td>
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<tr>
<td>Malignant tumor of breast</td>
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<td>1.5</td>
<td>-0.02</td>
<td>1.7</td>
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<tr>
<td>Hematologic neoplasm</td>
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<td>1.2</td>
<td>-0.01</td>
<td>1.4</td>
</tr>
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<td>0.2</td>
<td>0.00</td>
<td>0.3</td>
</tr>
<tr>
<td>Malignant neoplastic disease</td>
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<td>8.7</td>
<td>-0.01</td>
<td>10.8</td>
</tr>
<tr>
<td>Malignant tumor of colon</td>
<td>0.4</td>
<td>0.4</td>
<td>0.00</td>
<td>0.5</td>
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<tr>
<td>Malignant tumor of urinary bladder</td>
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<td>0.3</td>
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<td>0.3</td>
</tr>
<tr>
<td>Primary malignant neoplasm of prostate</td>
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<td>1</td>
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<td>15.5</td>
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<td>0.02</td>
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<td>0.03</td>
<td>16.2</td>
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<td>Drugs for acid related disorders</td>
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<td>Antinflammatory and antirheumatic products</td>
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<td>0.00</td>
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<td>Drugs used in diabetes</td>
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<td>8.2</td>
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<td>Antibacterials for systemic use</td>
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<td>21.5</td>
<td>-0.01</td>
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<td>7.1</td>
<td>0.02</td>
<td>10.3</td>
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<td>2.5</td>
<td>-0.01</td>
<td>3.2</td>
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<tr>
<td>Immunosuppressants</td>
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<td>Antiepileptics</td>
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<td>7.9</td>
<td>0.03</td>
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<tr>
<td>Psychotics</td>
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<td>10.6</td>
<td>0.02</td>
<td>15.9</td>
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<td>Antipsorias</td>
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<td>0.3</td>
<td>-0.01</td>
<td>0.4</td>
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<td>16.2</td>
<td>0.03</td>
<td>24.5</td>
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<td>Psychostimulants, agents used for adhd and nootropics</td>
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<td>3.2</td>
<td>0.01</td>
<td>4.9</td>
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https://mc.manuscriptcentral.com/bmj
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<th>Event</th>
<th>Database</th>
<th>N after PS matching</th>
<th>Person-years</th>
<th>Events</th>
<th>IR per 1,000 person-years (95% CI)</th>
<th>calibrated IRR (95% CI)</th>
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<td>Arterial thromboembolism (ATE)</td>
<td>CPRD UK</td>
<td>1,227,495</td>
<td>92,807</td>
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<tr>
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<td>1,886,308</td>
<td>140,256</td>
<td>416</td>
<td>2.97 (2.69-3.27)</td>
<td>0.85 (0.73-0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>204,702</td>
<td>15,530</td>
<td>44</td>
<td>2.83 (2.06-3.8)</td>
<td>Ref</td>
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<tr>
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<td>82,643</td>
<td>6,261</td>
<td>19</td>
<td>3.03 (1.83-4.74)</td>
<td>0.76 (0.41-1.39)</td>
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<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>CPRD UK</td>
<td>1,247,556</td>
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<td>DA Germany</td>
<td>1,912,752</td>
<td>142,268</td>
<td>193</td>
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<td>0.89 (0.71-1.11)</td>
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<tr>
<td></td>
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<td>1.31 (0.81-2)</td>
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<td>21</td>
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<td>2.62 (1.34-5.13)</td>
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<td>Intestinal infarction</td>
<td>CPRD UK</td>
<td>1,270,917</td>
<td>96,126</td>
<td>14</td>
<td>0.15 (0.08-0.24)</td>
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<tr>
<td></td>
<td>DA Germany</td>
<td>1,945,248</td>
<td>144,743</td>
<td>22</td>
<td>0.15 (0.1-0.23)</td>
<td>1.06 (0.53-2.13)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>CPRD UK</td>
<td>1,264,894</td>
<td>95,666</td>
<td>76</td>
<td>0.79 (0.63-0.99)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>DA Germany</td>
<td>1,936,816</td>
<td>144,104</td>
<td>75</td>
<td>0.52 (0.41-0.65)</td>
<td>0.66 (0.48-0.92)</td>
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<tr>
<td></td>
<td></td>
<td>210,616</td>
<td>15,982</td>
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<td>1.31 (0.81-2)</td>
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<tr>
<td>Myocardial infarction (MI)</td>
<td>CPRD UK</td>
<td>1,233,874</td>
<td>93,294</td>
<td>201</td>
<td>2.15 (1.87-2.47)</td>
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</tr>
<tr>
<td></td>
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<td>1,895,358</td>
<td>140,942</td>
<td>283</td>
<td>2.01 (1.78-2.26)</td>
<td>0.94 (0.78-1.14)</td>
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<td></td>
<td></td>
<td>208,975</td>
<td>15,856</td>
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<td>1.64 (1.07-2.4)</td>
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<tr>
<td>Pulmonary embolism (PE)</td>
<td>CPRD UK</td>
<td>1,254,781</td>
<td>94,894</td>
<td>197</td>
<td>2.08 (1.8-2.39)</td>
<td>Ref</td>
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<tr>
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<td>DA Germany</td>
<td>1,922,818</td>
<td>143,038</td>
<td>269</td>
<td>1.88 (1.66-2.12)</td>
<td>0.93 (0.77-1.12)</td>
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<tr>
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<td>212,362</td>
<td>16,115</td>
<td>20</td>
<td>1.24 (0.76-1.92)</td>
<td>Ref</td>
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<tr>
<td>Thrombocytopenia</td>
<td>CPRD UK</td>
<td>1,195,498</td>
<td>90,381</td>
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<td>4.89 (4.45-5.37)</td>
<td>Ref</td>
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<td></td>
<td>DA Germany</td>
<td>1,836,112</td>
<td>136,523</td>
<td>827</td>
<td>6.06 (5.65-6.48)</td>
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<td>15,516</td>
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<td>5.03 (3.97-6.27)</td>
<td>Ref</td>
</tr>
<tr>
<td>Any thrombosis (venous thrombo-embolism or arterial thromboembolism) with thrombocytopenia syndrome (Any-TTS)</td>
<td>CPRD UK</td>
<td>1,263,613</td>
<td>95,571</td>
<td>64</td>
<td>0.67 (0.52-0.86)</td>
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<tr>
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<td>Da Germany</td>
<td>1,934,651</td>
<td>143,950</td>
<td>121</td>
<td>0.84 (0.7-1)</td>
<td>1.29 (0.94-1.77)</td>
</tr>
<tr>
<td>Venous thrombo-embolism (VTE)</td>
<td>CPRD UK</td>
<td>1,233,788</td>
<td>93,290</td>
<td>314</td>
<td>3.37 (3-3.76)</td>
<td>Ref</td>
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<td></td>
<td>DA Germany</td>
<td>1,893,469</td>
<td>140,803</td>
<td>420</td>
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<td>209,244</td>
<td>15,878</td>
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<tr>
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<td>84,436</td>
<td>6,398</td>
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<td>3.91 (2.53-5.77)</td>
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<td>Thrombocytopenia</td>
<td>UK</td>
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<td></td>
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<td>38,474</td>
<td>230</td>
<td>5.98 (5.23-6.6)</td>
<td>0.94 (0.76-1.16)</td>
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</tbody>
</table>

**Table 5.** Incidence rates (IRs) per 1,000 person-years and incidence rate ratios (IRRs) for adenovirus vs mRNA-based vaccination in analyses that passed diagnostic tests among the matched cohorts.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Dataset</th>
<th>Total Events</th>
<th>Events</th>
<th>Incidence Rate (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Venous thromboembolism with thrombocytopenia syndrome (Any-TTS)</td>
<td>CPRD UK</td>
<td>1,076,722</td>
<td>64,277</td>
<td>0.65 (0.47-0.88)</td>
<td>1.16 (0.71-1.89)</td>
<td>Ref</td>
</tr>
<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>CPRD UK</td>
<td>1,063,064</td>
<td>63,456</td>
<td>1.51 (1.16-1.77)</td>
<td>Ref</td>
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<td>Pulmonary embolism (PE)</td>
<td>CPRD UK</td>
<td>1,069,375</td>
<td>63,835</td>
<td>1.44 (1.16-1.77)</td>
<td>Ref</td>
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</tr>
<tr>
<td>Venous thromboembolism (VTE)</td>
<td>CPRD UK</td>
<td>1,050,916</td>
<td>62,715</td>
<td>1.5 (1.17-1.96)</td>
<td>0.91 (0.64-1.3)</td>
<td>Ref</td>
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<tr>
<td>Ischaemic stroke</td>
<td>SIDIAP Spain</td>
<td>421,532</td>
<td>22,028</td>
<td>1.5 (1.03-2.1)</td>
<td>Ref</td>
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<tr>
<td>DVT</td>
<td>OpenClaims US</td>
<td>2,364,195</td>
<td>172,698</td>
<td>2.72 (2.48-2.98)</td>
<td>Ref</td>
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<tr>
<td>Pulmonary embolism (PE)</td>
<td>SIDIAP Spain</td>
<td>422,330</td>
<td>22,072</td>
<td>1.79 (0.86-3.29)</td>
<td>0.94 (0.45-1.96)</td>
<td>Ref</td>
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<td>Venous thromboembolism (VTE)</td>
<td>OpenClaims US</td>
<td>2,380,869</td>
<td>171,941</td>
<td>2.01 (1.8-2.23)</td>
<td>Ref</td>
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<tr>
<td>Arterial thromboembolism</td>
<td>OpenClaims US</td>
<td>2,365,254</td>
<td>172,778</td>
<td>1.9 (1.97-2.42)</td>
<td>Ref</td>
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<td>Thrombocytopenia</td>
<td>DA Germany</td>
<td>17,933</td>
<td>1,213</td>
<td>2.86 (1.56-4.8)</td>
<td>1.3 (0.57-2.93)</td>
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<td>Myocardial infarction (MI)</td>
<td>SIDIAP Spain</td>
<td>420,502</td>
<td>21,490</td>
<td>1.91 (1.38-2.59)</td>
<td>1.03 (0.55-1.93)</td>
<td>Ref</td>
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<td>Pulmonary embolism (PE)</td>
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<td>171,499</td>
<td>2.07 (1.8-2.34)</td>
<td>Ref</td>
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<td>Venous thromboembolism (VTE)</td>
<td>OpenClaims US</td>
<td>2,348,419</td>
<td>171,499</td>
<td>2.25 (1.81-2.69)</td>
<td>1.18 (0.7-1.98)</td>
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<tr>
<td>Ischaemic stroke</td>
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<td>21,749</td>
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<tr>
<td>Condition</td>
<td>Dataset</td>
<td>Count (Ref)</td>
<td>Count (Vaccine)</td>
<td>OR (95% CI)</td>
<td>p-value (95% CI)</td>
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</tr>
<tr>
<td>Deep vein thrombosis with thrombocytopenia syndrome (TTS-DVT)</td>
<td>OpenClaims US</td>
<td>2,271,774</td>
<td>172,851</td>
<td>0.07 (0.04-0.12)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>OpenClaims US</td>
<td>2,271,552</td>
<td>172,835</td>
<td>0.08 (0.04-0.14)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Any thrombosis (venous thromboembolism or arterial thromboembolism) with thrombocytopenia syndrome (Any-TTS)</td>
<td>OpenClaims US</td>
<td>2,232,550</td>
<td>169,861</td>
<td>2.24 (2.02-2.47)</td>
<td>Ref</td>
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<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>OpenClaims US</td>
<td>2,230,157</td>
<td>169,676</td>
<td>1.98 (1.77-2.2)</td>
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<td>Pulmonary embolism (PE)</td>
<td>OpenClaims US</td>
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<td>1.33 (1.16-1.51)</td>
<td>Ref</td>
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<td>Venous thromboembolism (VTE)</td>
<td>OpenClaims US</td>
<td>2,215,499</td>
<td>168,558</td>
<td>2.9 (2.64-3.16)</td>
<td>Ref</td>
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<td>Ischaemic stroke</td>
<td>OpenClaims US</td>
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<td>3.16 (2.9-3.44)</td>
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<td>Myocardial infarction (MI)</td>
<td>OpenClaims US</td>
<td>2,222,711</td>
<td>169,104</td>
<td>3.03 (2.78-3.31)</td>
<td>Ref</td>
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<td>Intestinal infarction</td>
<td>OpenClaims US</td>
<td>2,267,972</td>
<td>172,560</td>
<td>3.59 (3.07-4.18)</td>
<td>Ref</td>
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<td>Arterial thromboembolism (ATE)</td>
<td>OpenClaims US</td>
<td>2,171,445</td>
<td>165,188</td>
<td>13.6 (13.04-14.17)</td>
<td>Ref</td>
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<tr>
<td>Splanchnic and Visceral Thrombosis (SVT)</td>
<td>OpenClaims US</td>
<td>2,271,071</td>
<td>172,798</td>
<td>0.1 (0.06-0.16)</td>
<td>Ref</td>
<td></td>
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</table>

* Did not pass the systematic error diagnostic test of over 80% uncalibrated confidence intervals covering 1.

PS: propensity score
Table 6. Sensitivity analysis: Incidence rates (IR per 1,000 py) and IRR for adenovirus vs mRNA-based vaccination in analyses that passed diagnostics

<table>
<thead>
<tr>
<th>Sensitivity analysis 1: Thrombocytopenia window to 5 days before/after thrombosis post vaccination</th>
<th>Comparator</th>
<th>Target</th>
<th>Comparator</th>
<th>Target</th>
<th>Comparator</th>
<th>Target</th>
<th>Comparator</th>
<th>Target</th>
<th>Person-year</th>
<th>Event</th>
<th>IR per 1,000 py</th>
<th>RR calibrated</th>
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</thead>
<tbody>
<tr>
<td>CPRD AURUM</td>
<td>BNT162b2 1st dose</td>
<td>1,934,829</td>
<td>95,580</td>
<td>63</td>
<td>0.66 (0.51-0.84)</td>
<td></td>
<td>ChAdOx1 1st dose</td>
<td>1,934,829</td>
<td>143,963</td>
<td>120</td>
<td>0.83 (0.69-1)</td>
<td>1.3 (0.95-1.79)</td>
</tr>
<tr>
<td>Target</td>
<td>ChAdOx1 2nd dose</td>
<td>1,076,870</td>
<td>84,286</td>
<td>38</td>
<td>0.59 (0.42-0.81)</td>
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<td>Comparator</td>
<td>BNT162b2 2nd dose</td>
<td>1,934,829</td>
<td>143,963</td>
<td>120</td>
<td>0.83 (0.69-1)</td>
</tr>
<tr>
<td>J8_Open_Claims</td>
<td>Comparator</td>
<td>BNT162b2 1st dose</td>
<td>2,365,342</td>
<td>172,785</td>
<td>376</td>
<td>2.18 (1.96-2.41)</td>
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<td>Target</td>
<td>Janssen 1st dose</td>
<td>628,592</td>
<td>47,020</td>
<td>143</td>
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<td>Comparator</td>
<td>mRNA-1273 1st dose</td>
<td>2,232,627</td>
<td>169,867</td>
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<td>2.23 (2.01-2.46)</td>
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<td>Janssen 1st dose</td>
<td>628,758</td>
<td>47,030</td>
<td>143</td>
<td>3.04 (2.56-3.58)</td>
</tr>
<tr>
<td>Sensitivity analysis 2: Thrombocytopenia threshold of &lt;100,000 platelets per microliter</td>
<td>Comparator</td>
<td>mRNA-1273 1st dose</td>
<td>2,271,774</td>
<td>172,851</td>
<td>12</td>
<td>0.07 (0.04-0.12)</td>
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<td>Comparator</td>
<td>mRNA-1273 1st dose</td>
<td>2,271,552</td>
<td>172,835</td>
<td>14</td>
</tr>
<tr>
<td>J8_Open_Claims</td>
<td>Comparator</td>
<td>mRNA-1273 1st dose</td>
<td>2,232,550</td>
<td>169,861</td>
<td>380</td>
<td>2.24 (2.02-2.47)</td>
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<td>Target</td>
<td>Janssen 1st dose</td>
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<td>Comparator</td>
<td>mRNA-1273 1st dose</td>
<td>2,232,627</td>
<td>169,867</td>
<td>378</td>
<td>2.23 (2.01-2.46)</td>
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<td>Janssen 1st dose</td>
<td>639,432</td>
<td>47,838</td>
<td>11</td>
<td>0.23 (0.11-0.41)</td>
</tr>
<tr>
<td>Any TTS (VTE or ATE)</td>
<td>CPRD AURUM</td>
<td>BNT162b2 1st dose</td>
<td>1,263,960</td>
<td>95,597</td>
<td>83</td>
<td>0.66 (0.51-0.84)</td>
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<td>ChAdOx1 1st dose</td>
<td>1,935,138</td>
<td>143,986</td>
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<td>BNT162b2 2nd dose</td>
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<td>84,299</td>
<td>39</td>
<td>0.61 (0.43-0.83)</td>
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<td>ChAdOx1 2nd dose</td>
<td>795,893</td>
<td>41,094</td>
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<td>0.9 (0.63-1.24)</td>
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<tr>
<td>J8_Open_Claims</td>
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<td>2,356,254</td>
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<td>2.19 (1.97-2.42)</td>
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* did not pass the systematic error diagnostics of over 80% uncalibrated CIs cover 1.
### Tables

#### Supplementary Table 1. Negative control outcome concept list.

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<th>Concept Id</th>
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<td>Accidental poisoning by benzodiazepine-based tranquilizer</td>
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<tr>
<td>434455</td>
<td>Acquired claw toes</td>
</tr>
<tr>
<td>316215</td>
<td>Acquired spondylolisthesis</td>
</tr>
<tr>
<td>201612</td>
<td>Alcoholic liver damage</td>
</tr>
<tr>
<td>438730</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>441258</td>
<td>Anemia in neoplastic disease</td>
</tr>
<tr>
<td>316211</td>
<td>Acquired spondylolisthesis</td>
</tr>
<tr>
<td>192953</td>
<td>Intestinal adhesions with obstruction</td>
</tr>
<tr>
<td>196347</td>
<td>Intestinal parasitism</td>
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<tr>
<td>438730</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>137977</td>
<td>Jaundice</td>
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<tr>
<td>441258</td>
<td>Anemia in neoplastic disease</td>
</tr>
<tr>
<td>199764</td>
<td>Benign neoplasm of ovary</td>
</tr>
<tr>
<td>195596</td>
<td>Benign neoplasm of uterus</td>
</tr>
<tr>
<td>4145627</td>
<td>Benign neoplasm of ciliary body</td>
</tr>
<tr>
<td>4095292</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>77650</td>
<td>Aseptic necrosis of bone</td>
</tr>
<tr>
<td>4239673</td>
<td>Chronic salpingitis</td>
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<tr>
<td>4001454</td>
<td>Cervical spine ankylosis</td>
</tr>
<tr>
<td>4063241</td>
<td>Chronic instability of knee</td>
</tr>
<tr>
<td>195596</td>
<td>Chronic pancreatitis</td>
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<td>4206336</td>
<td>Chronic salpingitis</td>
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<tr>
<td>4093079</td>
<td>Seizure of left hand</td>
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<tr>
<td>442190</td>
<td>Hemorrhage of colon</td>
</tr>
<tr>
<td>4304827</td>
<td>High risk heterosexual behavior</td>
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<tr>
<td>194149</td>
<td>Hirschsprung’s disease</td>
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<td>443204</td>
<td>Human ehlers disease</td>
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<tr>
<td>403902</td>
<td>Hyperosmolar coma due to diabetes mellitus</td>
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<td>403787</td>
<td>Hyperosmolarity</td>
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### Supplementary Table 2. Cohort characteristics: European data (by database and cohorts)

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<th>Covariate</th>
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<th>Germany DA</th>
<th>SIDIAP</th>
<th>France LPD</th>
<th>IPCI</th>
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<td>nd.dose</td>
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<td>2nd.dose</td>
<td>1st.dose</td>
<td>2nd.dose</td>
<td>1st.dose</td>
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<tr>
<td>20-29 years</td>
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<td>0.1</td>
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<td>30-39 years</td>
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<tr>
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<td>60-69 years</td>
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<tr>
<td>70-79 years</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>80-89 years</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>90-99 years</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
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<td>Medical history</td>
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<tr>
<td>Charlson index</td>
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<td>141.1</td>
<td>131.1</td>
<td>140.1</td>
<td>140.1</td>
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<tr>
<td>- Romano adaptation</td>
<td>158.8</td>
<td>187.1</td>
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<td>165.4</td>
<td>109.1</td>
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<td>CHADS2VASc</td>
<td>128.3</td>
<td>216.2</td>
<td>200.6</td>
<td>219.9</td>
<td>196.9</td>
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<td>Acute respiratory disease</td>
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<td>59.6</td>
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</table>

**Notes:**
- **Cohort Count:** 3,789
- **Age group:** 1-10 years to 90-99 years
- **Medical history:** Charlson index, CHADS2VASc, Acute respiratory disease
|-----------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
### Supplementary Table 3. Cohort characteristics: US data

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<tr>
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<td>Viral hepatitis C</td>
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<td>0.2</td>
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<td>Visual system disorder</td>
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<td>Medication</td>
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<td>10.5</td>
</tr>
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<td>ANTIPILEPTICS</td>
<td>2.5</td>
<td>3.3</td>
</tr>
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<td>ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS</td>
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<td>DIURETICS</td>
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<td>DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES</td>
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<td>8</td>
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<td>9</td>
<td>1.9</td>
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<td>80 - 89</td>
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### Supplementary Table 4. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA LPD France

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<tr>
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</tr>
<tr>
<td><strong>ChAdOx1</strong></td>
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<td>11.7</td>
</tr>
<tr>
<td><strong>BNT162b2</strong></td>
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<td>2.8</td>
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<td><strong>SMD</strong></td>
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<td><strong>Malignant neoplastic disease</strong></td>
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<td><strong>Peripheral vascular disease</strong></td>
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<td><strong>Pneumonia</strong></td>
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<td><strong>Renal impairment</strong></td>
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<td><strong>Rheumatoid arthritis</strong></td>
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<tr>
<td><strong>Schizophrenia</strong></td>
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<td>0.5</td>
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**Medication**

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<th>Before PS matching</th>
<th>After PS matching</th>
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</thead>
<tbody>
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<td><strong>BNT162b2</strong></td>
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<td><strong>SMD</strong></td>
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**Supplementary Table 4. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA LPD France**
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<th>Age Group</th>
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<td>90 - 99</td>
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| Gender: female | 47.6, 56.4, -0.17, 54.5, 54.2, 0.00 |

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<tr>
<td>Chronic obstructive lung disease</td>
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<td>Crohn’s disease</td>
<td>0.2, 0.4, -0.03, 0.3, 0.3, -0.01</td>
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<td>Dementia</td>
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<td>Depressive disorder</td>
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<td>Diabetes mellitus</td>
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<td>Gastroesophageal reflux disease</td>
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<td>Gastrointestinal hemorrhage</td>
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<td>Osteoarthritis</td>
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<td>Pneumonia</td>
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<td>Urinary tract infectious disease</td>
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<td>Viral hepatitis C</td>
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### Visual system disorder

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### Medical history: Cardiovascular disease

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<tr>
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<tr>
<td>Coronary arteriosclerosis</td>
<td>2.2</td>
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<tr>
<td>Heart disease</td>
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<td>18.1</td>
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<tr>
<td>Heart failure</td>
<td>1.2</td>
<td>2.1</td>
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<tr>
<td>Ischemic heart disease</td>
<td>4.9</td>
<td>4.8</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>1.6</td>
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<td>Pulmonary embolism</td>
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<td>1.1</td>
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<td>Venous thrombosis</td>
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### Medical history: Neoplasms

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<td>Malignant lymphoma</td>
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<tr>
<td>Malignant neoplasm of anorectum</td>
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<td>0.9</td>
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<tr>
<td>Malignant neoplastic disease</td>
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<td>Malignant tumor of breast</td>
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<tr>
<td>Malignant tumor of colon</td>
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<tr>
<td>Malignant tumor of urinary bladder</td>
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### Medication use

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<td>Antineoplastic agents</td>
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<td>Beta blocking agents</td>
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<td>Drugs for acid related disorders</td>
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<td>Drugs used in diabetes</td>
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<td>Immunosuppressants</td>
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<td>Psychleptics</td>
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<td>Psychostimulants, agents used for adhd and nootropics</td>
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Supplementary Table 5. Baseline characteristics of eligible cohorts of vaccinated people identified in IPCI

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<table>
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<th>ChAdOx1 %</th>
<th>BNT162b2 %</th>
<th>ChAdOx1 SMD</th>
<th>BNT162b2 SMD</th>
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<td>Gastrointestinal hemorrhage</td>
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<td>5.8</td>
<td>0.01</td>
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<td>Human immunodeficiency virus infection</td>
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<td>0.03</td>
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<td>0.02</td>
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<td>-0.09</td>
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<td>0.06</td>
<td>0.8</td>
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<td>-0.04</td>
<td>8.2</td>
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<td>-0.01</td>
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<td>-0.01</td>
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</table>

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### Supplementary Table 6. Baseline characteristics of eligible cohorts of vaccinated people identified in IQVIA US Hospital CDM

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<th>BNT162b2</th>
<th>SMD</th>
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<th>BNT162b2</th>
<th>SMD</th>
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</tr>
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<th>2&lt;sup&gt;nd&lt;/sup&gt; dose ChAdOx1 vs BNT162b2</th>
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<td>✓</td>
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<td>x</td>
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<td>Power</td>
<td>MDRR&lt;5 for 1+ outcomes</td>
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<td>0</td>
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<td>0</td>
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<td>n/a</td>
<td>$</td>
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<td>$</td>
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<tr>
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<td>n/a</td>
<td>n/a</td>
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<tr>
<td></td>
<td>Power</td>
<td>MDRR&lt;5 for 1+ outcomes</td>
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Systematic error  <20% associated w exposure  n/a  n/a  n/a  n/a  72.2%  67.9%

IQVIA US HOSPITAL CDM

Covariate balance  SMD<0.1 for all  n/a  n/a  n/a  n/a  n/a

Power  MDRR<5 for 1+ outcomes  n/a  n/a  n/a  n/a  0  0

Systematic error  <20% associated w exposure  n/a  n/a  n/a  n/a  $  $

Grey = 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. $: empirical calibration was not conducted due to insufficient NCOs estimated.

Supplementary Table 8. Crude incidence rate and corresponding 95% confidence intervals, European data

<table>
<thead>
<tr>
<th>Vaccine</th>
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<th>Germany DA</th>
<th>SIDIAP</th>
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</thead>
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<td>N</td>
<td>Person-year</td>
<td>Events</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>ChAdOx1 1st dose</td>
<td>3,621,898</td>
<td>263,673</td>
<td>1,261</td>
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<tr>
<td>ChAdOx1 2nd dose</td>
<td>1,115,370</td>
<td>54,189</td>
<td>347</td>
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<tr>
<td>BNT162b2 1st dose</td>
<td>1,724,118</td>
<td>138,755</td>
<td>98</td>
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<tr>
<td>BNT162b2 2nd dose</td>
<td>1,358,901</td>
<td>86,349</td>
<td>458</td>
</tr>
<tr>
<td>mRNA -1273 1st dose</td>
<td>653</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>mRNA -1273 2nd dose</td>
<td>72</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Janssen COVID-19</td>
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Any thrombosis (venous thromboembolism or arterial thromboembolism) with thrombocytopenia syndrome (Any-TTS)

<table>
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<th>Vaccine</th>
<th>UK CPRD</th>
<th>Germany DA</th>
<th>SIDIAP</th>
</tr>
</thead>
<tbody>
<tr>
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<td>N</td>
<td>Person-year</td>
<td>Events</td>
</tr>
<tr>
<td>ChAdOx1 1st dose</td>
<td>3,621,898</td>
<td>263,673</td>
<td>1,261</td>
</tr>
<tr>
<td>ChAdOx1 2nd dose</td>
<td>1,115,370</td>
<td>54,189</td>
<td>347</td>
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<tr>
<td>BNT162b2 1st dose</td>
<td>1,724,118</td>
<td>138,755</td>
<td>98</td>
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<tr>
<td>BNT162b2 2nd dose</td>
<td>1,358,901</td>
<td>86,349</td>
<td>458</td>
</tr>
<tr>
<td>mRNA -1273 1st dose</td>
<td>653</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>mRNA -1273 2nd dose</td>
<td>72</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Janssen COVID-19</td>
<td>18,763</td>
<td>1,272</td>
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</table>

Deep vein thrombosis with thrombocytopenia syndrome (TTS-DVT)
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Event</th>
<th>Rate (95% CI)</th>
<th><em>p</em>-value</th>
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<tbody>
<tr>
<td>mRNA -1273 1st dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>mRNA -1273 2nd dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>BNT162b2 1st dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>BNT162b2 2nd dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>ChAdOx1 1st dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>ChAdOx1 2nd dose</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
<tr>
<td>Janssen COVID-19</td>
<td>Venous thrombo-embolism with thrombocytopenia syndrome (TTS-VTE)</td>
<td>18,758 (72.72)</td>
<td>0.05 (0.02-0.07)</td>
</tr>
</tbody>
</table>

*Note: TTS-VTE = Venous thrombo-embolism with thrombocytopenia syndrome*
mRNA -1273 1st dose 1,783,357 6,649 0.15 0.07-0.31 178,246 9,389 25 0.08 (0.04-0.16)

mRNA -1273 2nd dose 1,783,357 6,649 0.15 0.07-0.31 178,246 9,389 25 0.08 (0.04-0.16)

Janssen COVID-19 16,762 1,272 <5 126,938 6,033 0 0 (0.06-0.16)

Deep vein thrombosis (DVT)

ChAdOx1 1st dose 3,741,359 272,472 335 1.21 (1.1-1.37) 88,463 6,706 21 3.13 (1.94-4.79)

ChAdOx1 2nd dose 1,169,773 57,025 86 1.51 (1.21-1.86) 16,390 1,288 0 0 (0.26-0.66)

BNT162B2 1st dose 1,004,763 130,994 236 1.72 (1.51-1.96) 344,916 25,992 33 1.77 (0.79-1.87) 1,973,028 125,127 219 1.75 (1.53-2)

BNT162B2 2nd dose 1,341,717 84,648 143 1.69 (1.42-1.99) 181,988 12,970 <5 2.13 (1.41-3.11) 1,312,985 88,727 170 1.92 (1.64-2.33)

mRNA -1273 1st dose 634 47 <5 4,573,771 6,169 71 2.04 (1.43-2.83)

mRNA -1273 2nd dose 71 5 0 0 (0.70-0.69) 182,802 9,759 26 2.68 (1.74-3.5)

Janssen COVID-19 18,465 1,252 <5 126,189 8,072 10 1.66 (0.8-3.06)

Venous thrombo-embolism (VTE)

ChAdOx1 1st dose 3,715,771 273,676 387 1.41 (1.28-1.56) 88,838 6,734 6 0.89 (0.33-1.94)

ChAdOx1 2nd dose 1,176,965 59,391 70 1.22 (0.95-1.54) 18,500 1,296 <5

BNT162B2 1st dose 1,815,494 137,808 275 2.17 (1.72-2.5) 353,848 28,017 30 1.38 (0.97-1.92) 1,978,276 125,496 177 1.41 (1.21-1.63)

BNT162B2 2nd dose 1,349,726 85,156 122 1.43 (1.19-1.71) 177,697 12,657 20 1.56 (1.26-2.44) 1,317,982 88,043 131 1.47 (1.23-1.75)

mRNA -1273 1st dose 643 48 0 0 (0.75-0.69) 244,418 17,674 48 2.72 (2.00-3.69)

mRNA -1273 2nd dose 71 5 0 0 (0.70-0.69) 183,339 9,793 23 2.35 (1.49-3.52)

Janssen COVID-19 18,581 1,259 <5 126,442 8,024 5 0.83 (0.27-2.94)

Ischaemic stroke

ChAdOx1 1st dose 3,776,958 275,163 95 0.35 (0.28-0.42) 86,152 6,682 13 1.95 (1.04-3.3)

ChAdOx1 2nd dose 1,187,113 57,901 33 0.57 (0.39-0.86) 18,246 1,278 0 0 (0.28-0.89)

BNT162B2 1st dose 1,829,892 138,990 118 0.89 (0.71-1.12) 341,248 25,927 26 1.01 (0.68-1.47) 1,935,388 122,252 549 4.40 (3.12-6.58)

BNT162B2 2nd dose 1,360,485 85,825 52 0.61 (0.45-0.75) 176,358 12,574 8 0.64 (0.27-1.25) 1,276,052 85,949 523 6.08 (5.57-6.63)

mRNA -1273 1st dose 629 47 <5 242,160 17,541 79 4.5 (3.57-5.61)

mRNA -1273 2nd dose 70 5 0 0 (0.71-0.69) 181,795 9,691 42 4.33 (3.12-5.86)

Janssen COVID-19 16,332 1,241 8 0.45 (1.78-12.7) 125,850 9,982 14 2.34 (1.28-3.52)

Myocardial infarction

ChAdOx1 1st dose 3,727,073 271,378 422 1.56 (1.41-1.71) 87,339 6,620 10 1.51 (0.72-2.78)

ChAdOx1 2nd dose 1,155,608 56,294 85 1.51 (1.21-1.87) 17,915 1,253 <5

BNT162B2 1st dose 1,783,357 138,990 118 0.89 (0.71-1.12) 341,248 25,927 26 1.01 (0.68-1.47) 1,935,388 122,252 549 4.40 (3.12-6.58)

BNT162B2 2nd dose 1,324,606 83,538 158 1.89 (1.61-2.1) 174,395 12,425 24 1.93 (1.24-2.87) 1,297,110 87,586 269 3.07 (2.72-3.46)

mRNA -1273 1st dose 645 48 0 0 (0.75-0.69) 242,726 17,546 30 1.71 (1.15-2.44)

mRNA -1273 2nd dose 71 5 0 0 (0.70-0.69) 181,881 9,716 21 2.16 (1.34-3.3)

Janssen COVID-19 18,277 1,236 <5 125,219 9,951 10 1.68 (0.81-3.09)

Intestinal infarction

mRNA -1273 1st dose 653 49 0 0 (0.74-7.7) 246,081 17,797 0 0 (0.0-2.21)

mRNA -1273 2nd dose 72 5 0 0 (0.69-5.52) 184,775 9,889 <5

Janssen COVID-19 16,762 1,272 <5 126,938 6,033 0 0 (0.06-0.16)
## Supplementary Table 9. Crude incidence rate and corresponding 95% confidence intervals, US data

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<th>Vaccine</th>
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<td>Janssen COVID-19</td>
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<td>TTS_MI</td>
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<td>mRNA-1273 1st dose</td>
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</tr>
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<td>1,443</td>
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<tr>
<td>Janssen COVID-19</td>
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<tr>
<td>TTS_PE</td>
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<tr>
<td>Janssen COVID-19</td>
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</tr>
<tr>
<td>TTS_VTE</td>
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<tr>
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<td>1,443</td>
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<tr>
<td>Janssen COVID-19</td>
<td>1,713</td>
<td>119</td>
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<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>BNT162b2 1st dose</td>
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<tr>
<td>BNT162b2 2nd dose</td>
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<td>5,484</td>
</tr>
<tr>
<td>mRNA-1273 1st dose</td>
<td>62,776</td>
<td>4,730</td>
</tr>
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<td>mRNA-1273 2nd dose</td>
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<tr>
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<td>Splanchnic and Visceral Thrombosis</td>
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<td>mRNA-1273 1st dose</td>
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<tr>
<td>Intestinal infarction</td>
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<td>Myocardial infarction</td>
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<td>Arterial thromboembolism</td>
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</table>

Confidential: For Review Only
### Supplementary Table 10. Incidence rates before- and after- propensity score matching.

<table>
<thead>
<tr>
<th>Database</th>
<th>Vaccine</th>
<th>IR pre-matching</th>
<th>IR after-matching</th>
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### Supplementary Table 11. Age and sex stratified incidence rate ratio, CPRD UK.

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<td>1.16 (0.81-1.69)</td>
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<td>1.39 (1.12-1.73)</td>
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<td>ChAdOx1 vs. BNT162b2 1st dose</td>
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<td>1.49 (1.23-1.81)</td>
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<td>ChAdOx1 vs. BNT162b2 2nd dose</td>
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<td>ChAdOx1 vs. BNT162b2 1st dose</td>
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<td>1.55 (0.64-3.72)</td>
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<td>ChAdOx1 vs. BNT162b2 1st dose</td>
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<td>1.02 (0.39-2.65)</td>
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<td>0.68 (0.44-1.05)</td>
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### Supplementary Table 12. Age and sex stratified incidence rate ratio, US Open Claims.

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<th>Subgroup</th>
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<th>IRR</th>
<th>calibrated IRR</th>
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<td>3.95</td>
<td>5.89 (2.78-12.82)</td>
<td><strong>4.64 (2.16-9.97)</strong></td>
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<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
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<td>0.74 (0.26-2.09)</td>
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<td><strong>0.58 (0.36-0.95)</strong></td>
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<td>Janssen COVID-19 vs. BNT162b2 2nd dose</td>
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<td>1.17</td>
<td>1.23 (1.11-1.37)</td>
<td>0.93 (0.58-1.5)</td>
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<td>Janssen COVID-19 vs. BNT162b2 2nd dose</td>
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<td>0.80 (0.68-1.34)</td>
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<td>age group: 20 - 29</td>
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<td>6.01 (2.83-13.43)</td>
<td><strong>5.1 (1.71-15.19)</strong></td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
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<td>0.96 (0.64-1.56)</td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
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<td>0.7 (0.29-1.67)</td>
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<td>0.97 (0.52-1.82)</td>
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<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
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<td>0.96</td>
<td>(0.67-1.35)</td>
<td>0.57 (0.24-1.35)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 80 - 89</td>
<td>1.84</td>
<td>1.09</td>
<td>(0.71-1.63)</td>
<td>0.82 (0.27-2.49)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>gender = male</td>
<td>1.43</td>
<td>1.48</td>
<td>(1.17-1.85)</td>
<td>1.63 (1.58)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>gender = female</td>
<td>1.42</td>
<td>1.15</td>
<td>(0.91-1.45)</td>
<td>0.82 (0.45-1.51)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 30 - 39</td>
<td>3.69</td>
<td>2.06</td>
<td>(0.91-4.36)</td>
<td>1.41 (0.56-3.56)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 40 - 49</td>
<td>3.08</td>
<td>1.8</td>
<td>(0.88-3.46)</td>
<td>1.05 (0.31-3.53)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 50 - 59</td>
<td>2.21</td>
<td>1.7</td>
<td>(1.02-2.74)</td>
<td>1.2 (0.51-2.83)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 60 - 69</td>
<td>2.04</td>
<td>0.95</td>
<td>(0.56-1.54)</td>
<td>0.79 (0.38-1.66)</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 70 - 79</td>
<td>2.08</td>
<td>1.74</td>
<td>(1.08-2.75)</td>
<td>1.14 (0.47-2.77)</td>
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</tbody>
</table>
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 80 - 89 | 3.47 | 1.52 (0.65-3.3) | 1.18 (0.46-3.06) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | gender = MALE | 1.68 | 1.45 (1.04-2) | 1.1 (0.62-1.95) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | gender = FEMALE | 1.65 | 1.53 (1.1-2.08) | 1.18 (0.65-2.13) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 30 - 39 | 4.14 | 2.86 (1.2-6.7) | 1.57 (0.65-3.81) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 40 - 49 | 3.26 | 2 (0.93-4.19) | 1.07 (0.31-3.62) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 50 - 59 | 2.15 | 1.56 (0.94-2.5) | 1.07 (0.46-2.48) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 60 - 69 | 2.08 | 1.07 (0.63-1.74) | 0.88 (0.51-1.52) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 70 - 79 | 2.21 | 2.27 (1.36-3.76) | 1.35 (0.53-3.42) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 80 - 89 | 3.45 | 1.68 (0.75-3.36) | 1.26 (0.34-4.63) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | gender = MALE | 1.69 | 1.52 (1.08-2.11) | 1.03 (0.61-1.73) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | gender = FEMALE | 1.68 | 1.72 (1.24-2.36) | 1.24 (0.65-2.36) | 0

**Thrombocytopenia**

Janssen COVID-19 vs. BNT162b2 1st dose | age group: 20 - 29 | 4.21 | 1.62 (0.61-3.82) | 1.27 (0.48-3.39) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 30 - 39 | 3.31 | 1.98 (0.95-3.82) | 1.35 (0.57-3.2) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 40 - 49 | 2.43 | 3.06 (1.7-5.2) | 1.79 (0.59-5.45) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 50 - 59 | 1.73 | 1.55 (1.08-2.18) | 1.09 (0.5-2.38) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 60 - 69 | 1.67 | 1.09 (0.76-1.54) | 0.91 (0.49-1.71) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 70 - 79 | 1.89 | 0.79 (0.47-1.25) | 0.52 (0.21-1.28) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 80 - 89 | 2.12 | 0.93 (0.52-1.55) | 0.72 (0.35-1.46) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | gender = MALE | 1.43 | 1.33 (1.05-1.68) | 1.01 (0.6-1.7) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | gender = FEMALE | 1.5 | 1.26 (0.96-1.64) | 0.97 (0.55-1.71) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 20 - 29 | 3.2 | 1.03 (0.41-2.23) | 0.87 (0.26-2.91) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 30 - 39 | 3.4 | 2.09 (0.97-4.28) | 1.15 (0.52-2.52) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 40 - 49 | 2.37 | 2.88 (1.7-4.86) | 1.53 (0.52-4.54) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 50 - 59 | 1.71 | 1.43 (1.2-2.01) | 0.98 (0.46-2.1) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 60 - 69 | 1.67 | 1.07 (0.74-1.5) | 0.88 (0.5-1.39) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 70 - 79 | 1.94 | 0.92 (0.56-1.46) | 0.55 (0.22-1.39) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | gender = MALE | 1.43 | 1.37 (1.08-1.73) | 0.93 (0.58-1.48) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | gender = FEMALE | 1.47 | 1.12 (0.85-1.44) | 0.8 (0.43-1.49) | 0

**TTS any**

Janssen COVID-19 vs. BNT162b2 1st dose | age group: 30 - 39 | 3.59 | 2.38 (1.13-4.69) | 1.63 (0.68-3.89) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 40 - 49 | 2.59 | 2.49 (1.38-4.47) | 1.46 (0.47-4.56) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 50 - 59 | 1.87 | 1.58 (1.06-2.32) | 1.12 (0.5-2.49) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 60 - 69 | 1.75 | 1.16 (0.79-1.67) | 0.97 (0.51-1.84) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 70 - 79 | 2.05 | 0.92 (0.53-1.5) | 0.6 (0.24-1.52) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | age group: 80 - 89 | 2.31 | 1.23 (0.69-2.11) | 0.96 (0.46-1.97) | 1
Janssen COVID-19 vs. BNT162b2 1st dose | gender = MALE | 1.48 | 1.52 (1.18-1.94) | 1.15 (0.68-1.95) | 0
Janssen COVID-19 vs. BNT162b2 1st dose | gender = FEMALE | 1.58 | 1.21 (0.89-1.63) | 0.94 (0.52-1.68) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 20 - 29 | 4.04 | 1.05 (0.34-2.64) | 0.89 (0.23-3.5) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 30 - 39 | 3.56 | 2.38 (1.09-4.9) | 1.3 (0.59-2.88) | 1
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 40 - 49 | 2.59 | 2.61 (1.45-4.65) | 1.39 (0.45-4.25) | 0
Janssen COVID-19 vs. mRNA-1273 1st dose | age group: 50 - 59 | 1.86 | 1.57 (1.05-2.33) | 1.08 (0.49-2.37) | 0
<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Age Group</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 60 - 69</td>
<td>1.77</td>
<td>1.22 (0.82-1.77)</td>
<td>1 (0.66-1.52)</td>
<td>1</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 70 - 79</td>
<td>2.02</td>
<td>0.93 (0.54-1.51)</td>
<td>0.55 (0.21-1.43)</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 80 - 89</td>
<td>2.32</td>
<td>1.29 (0.72-2.19)</td>
<td>0.97 (0.3-3.13)</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>gender = MALE</td>
<td>1.49</td>
<td>1.65 (1.28-2.11)</td>
<td>1.12 (0.7-1.79)</td>
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<tr>
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<td>gender = FEMALE</td>
<td>1.55</td>
<td>1.08 (0.79-1.44)</td>
<td>0.77 (0.41-1.46)</td>
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<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>gender = MALE</td>
<td>1.49</td>
<td>1.65 (1.28-2.11)</td>
<td>1.12 (0.7-1.79)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>gender = FEMALE</td>
<td>1.55</td>
<td>1.08 (0.79-1.44)</td>
<td>0.77 (0.41-1.46)</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Age Group</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 30 - 39</td>
<td>3.18</td>
<td>2.1 (1.06-3.94)</td>
<td>1.44 (0.64-3.26)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 40 - 49</td>
<td>2.23</td>
<td>1.41 (0.82-2.31)</td>
<td>0.82 (0.27-2.5)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 50 - 59</td>
<td>1.77</td>
<td>1.23 (0.83-1.77)</td>
<td>0.87 (0.39-1.92)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 60 - 69</td>
<td>1.6</td>
<td>1.19 (0.86-1.62)</td>
<td>1.55 (0.83-1.26)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 70 - 79</td>
<td>1.73</td>
<td>1.48 (1.02-2.09)</td>
<td>0.96 (0.42-2.22)</td>
<td>0</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>age group: 80 - 89</td>
<td>2.24</td>
<td>1.06 (0.59-1.81)</td>
<td>0.82 (0.41-1.69)</td>
<td>1</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>gender = MALE</td>
<td>1.45</td>
<td>1.34 (1.05-1.7)</td>
<td>1.01 (0.61-1.72)</td>
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<tr>
<td>Janssen COVID-19 vs. BNT162b2 1st dose</td>
<td>gender = FEMALE</td>
<td>1.43</td>
<td>1.34 (1.06-1.68)</td>
<td>1.03 (0.61-1.79)</td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 30 - 39</td>
<td>2.64</td>
<td>1.31 (0.67-2.42)</td>
<td>0.72 (0.36-1.44)</td>
<td>1</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 40 - 49</td>
<td>2.45</td>
<td>1.91 (1.08-3.31)</td>
<td>1.02 (0.34-3.09)</td>
<td>0</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 50 - 59</td>
<td>1.77</td>
<td>1.24 (0.84-1.79)</td>
<td>0.85 (0.39-1.85)</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 60 - 69</td>
<td>1.61</td>
<td>1.27 (0.92-1.72)</td>
<td>1.04 (0.74-1.47)</td>
<td>1</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 70 - 79</td>
<td>1.71</td>
<td>1.4 (0.98-1.98)</td>
<td>0.83 (0.35-1.96)</td>
<td>0</td>
</tr>
<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>age group: 80 - 89</td>
<td>2.35</td>
<td>1.42 (0.82-2.37)</td>
<td>1.06 (0.33-3.42)</td>
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<tr>
<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
<td>gender = MALE</td>
<td>1.44</td>
<td>1.26 (0.99-1.6)</td>
<td>0.85 (0.53-1.36)</td>
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<td>Janssen COVID-19 vs. mRNA-1273 1st dose</td>
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<td>1.45</td>
<td>1.52 (1.2-1.92)</td>
<td>1.09 (0.59-2.01)</td>
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### Supplementary Table 13. Cohort selection and minimal detectable relative risk, database-target-outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Original cohort</th>
<th>Target</th>
<th>Without prior outcomes</th>
<th>With at least 1 days at risk</th>
<th>Matched on propensity score</th>
<th>MDRR</th>
<th>Include in meta-analysis</th>
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Supplementary Table 14. List of covariates with top 10 highest absolute value of propensity score model coefficient.

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**Germany_DA - ChAdOx1 1st dose - BNT162b2 1st dose**

| Germany_DA - Janssen COVID-19 - BNT162b2 1st dose                | 5.92 |
| index month: 8                                                  |      |
| index month: 7                                                  |      |
| index month: 3                                                  |        | measurement distinct concept count during day -180 through -4 concept_count relative to index | 4.77 |
| age group: 10 - 19                                              | -1.77| index month: 5 | 4.66 |
| index month: 9                                                  | -1.63| index month: 7 | 4.53 |
| gender = MALE                                                  | 1.44 | index month: 9 | 4.06 |
| index month: 6                                                  | -1.42| Charlon index - Romano adaptation | 2.25 |
| drug_era distinct concept count during day -180 through -4 concept_count relative to index | -1.24| drug_era distinct concept count during day -180 through -4 concept_count relative to index | 2.02 |
| index month: 4                                                  | -1.22| gender = FEMALE |      |
| age group: 20 - 29                                              | -1.05| age group: 10 - 19 | -1.75 |

**Germany_DA - ChAdOx1 2nd dose - BNT162b2 2nd dose**

| SIDIAP - Janssen COVID-19 - BNT162b2 1st dose                   | 10.04 |
| index month: 4                                                  |      |
| index month: 5                                                  |        | CHADS2VASc | -10.04 |
| age group: 10 - 19                                              | -2.20| index month: 1 | -6.91 |
| index month: 9                                                  | -2.64| index month: 3 | -6.24 |
| drug_era distinct concept count during day -180 through -4 concept_count relative to index | -1.67| index month: 2 | -6.00 |
| age group: 30 - 39                                              | -1.44| index month: 12 |        |
| drug_era group during day -180 through -4 days relative to index: ascorbic acid | 1.39| visit_occurrence concept count during day -180 through -4 concept_count relative to index: Telehealth | -3.95 |
| age group: 20 - 29                                              | -1.37| age group: 60 - 69 | 3.75 |
| condition_era group during day -9999 through -4 days relative to index: Attention deficit hyperactivity disorder | -1.25| age group: 70 - 79 | 2.75 |
| age group: 40 - 49                                              | -1.24| visit_occurrence concept count during day -180 through -4 concept_count relative to index: Outpatient Visit | 2.56 |
| visit_occurrence concept count during day -180 through -4 concept_count relative to index: Office Visit | 1.14| condition_era group during day -9999 through -4 days relative to index: Transient cerebral ischemia | 1.95 |

**US_Open_Claims - Janssen COVID-19 - BNT162b2 1st dose**

<p>| US_Open_Claims - Janssen COVID-19 - mRNA-1273 1st dose       | 8.60 |
| index month: 1                                               | -9.36| index month: 1 |      |
| index month: 2                                               | -7.67| index month: 2 | -7.62 |</p>
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Charlson index - Romano adaptation: 1.28
Figures

Figure 1. Passed systematic error diagnostic: <20% negative control outcomes associated with exposure in the uncalibrated analyses (CPRD Aurum, 1st dose ChAdOx1 vs BNT162b2)

Estimates below the diagonal dashed lines are statistically significant (alpha = 0.05) different from the true effect size (expected IRR=1). A well-calibrated estimator should have the true effect size within the 95 percent confidence interval 95 percent of times.
Figure 2. 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 BNT162b2

Figure 8b. Systematic error in the analysis of Janssen vs 1-dose mRNA-1273