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Risk of thrombosis with thrombocytopaenia syndrome (TTS) after vaccination with AZD1222: a European VAC4EU post-authorisation safety study

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ABSTRACT

A post-authorisation safety study was conducted for the AZD1222 COVID-19 vaccine. This paper presents one study outcome, thrombosis with thrombocytopenia syndrome (TTS), and estimates TTS risk in subjects administered ≥1 AZD1222 dose versus concurrent unvaccinated, pre-pandemic historical, or mRNA-vaccinated subjects.

The cohort study used data from CPRD Aurum (UK), VID (Spain), SIDIAP (Spain) and PHARMO-GP database (PHARMO) (the Netherlands). AZD1222-vaccinated subjects were matched on age, sex, region, prior COVID-19, and special population status. Incident venous TTS was defined as a thromboembolic event and thrombocytopaenia within ±10 days and no TTS within the prior year.

5,321,930 subjects were matched with concurrent unvaccinated comparators, 4,831,010 with historical comparators, and 4,028,091 with mRNA active comparators (CPRD only). In CPRD, 83% of subjects were vaccinated in Q1 2021; 64% were < 60 years. In VID, SIDIAP, and PHARMO, >59% were vaccinated after Q1 2021; most subjects were ≥ 60 years. Propensity score–weighted incidence rate ratios (IRRs) (95% confidence

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intervals) for TTS were CPRD, 1.14 (0.60–2.17); VID, 0.34 (0.10–1.18); SIDIAP, 0.66 (0.33–1.34); and zero events in PHARMO. Incidence rates (IRs) and IRRs for TTS, where available, were higher in AZD1222-vaccinated versus concurrent unvaccinated subjects <60 years or during shorter risk windows. After case validation, positive predictive value–adjusted IRRs were < 1. For historical comparators, meta-analysis resulted in an IRR of 1.78 (95% CI,1.12–2.82; $I^2 = 0\%$). For mRNA active comparators, the IRR was 1.12 (95% CI,0.61–2.05).

Considering the magnitude, precision, and potential biases—such as selection bias due to informative censoring and potential outcome misclassification—the totality of evidence suggests a possible increased risk of TTS with post-AZD1222 vaccination that may be higher among subjects <60 years and 1–42 days after first AZD1222 dose, in line with the literature. Differential age distributions resulting from country-level differences in the risk minimisation measures may explain IRR disparities across data sources.

1. Introduction

AZD1222 (called VAXZEVRIA™ in Europe) is a vaccine that was developed to prevent coronavirus disease 2019 (COVID-19). On 30 December 2020, the Medicines and Healthcare products Regulatory Agency in the United Kingdom (UK) provided authorisation for an emergency supply of AZD1222, and on 29 January 2021, the European Commission granted conditional marketing authorisation for the vaccine [1]. The vaccination course consisted of 2 intramuscular injections administered 28 to 84 days apart. Since May 2022, a third dose may have been given at least 3 months after the second dose. On 7 May 2024, the marketing authorisations in the European Union and UK were withdrawn [1].

Vaccination policies that steered AZD1222 into specific age and special population categories varied over time. A key event for AZD1222 was the signal of potential increased risk of thrombosis with thrombocytopaenia syndrome (TTS) identified in March 2021. Risk minimisation measures were implemented throughout Europe, primarily to restrict use of AZD1222 to certain age groups. Vaccination with AZD1222 was restricted in the UK in April 2021 to adults over 30 years of age, in Spain in March 2021 to adults aged ≥60 years, and in the Netherlands in March 2021 to adults aged 60 to 64 years and healthcare staff. Later, the restrictions were adjusted to adults aged 60 to 69 years in Spain and to adults aged 60 to 75 years in the Netherlands.

An observational post-authorisation safety study (PASS), required in AstraZeneca's approved European Union risk management plan, was conducted to evaluate 40 adverse events of special interest, including TTS, after vaccination with AZD1222. In this manuscript, we focus on the risk of TTS in subjects who received at least 1 dose of AZD1222 compared with concurrent unvaccinated subjects (primary objective), pre-COVID-19 pandemic historical comparators, and mRNA active comparators (exploratory objectives). The protocol and the final report of this PASS are publicly available (https://catalogues.ema.europa.eu/node/3319/administrative-details).

2. Materials and methods

2.1. Study design and setting

A multi-country, multi-database cohort design was used to estimate the incidence of TTS among subjects who received AZD1222 compared with subjects in 3 different comparator cohorts: concurrent unvaccinated comparators, historical comparators, and COVID-19 mRNA active comparators. This study was conducted by partners within the Vaccine monitoring Collaboration for Europe (VAC4EU) association (https://vac4eu.org/) and used a common protocol across all study sites, the ConcePTION common data model [2] for syntactic harmonisation, the metadata tables described in RWE-BRIDGE [3] and VAC4EU Codemapper codelist methodology [4] for semantic harmonisation, and the INSIGHT Level 1–2 data quality checks [5], followed by common analytical scripts. The study period started on 4 January 2021, when the vaccine was first used in the UK, and ended at the latest on 31 December 2022 (or last data available in the data source). The study was conducted using multiple secondary automated electronic healthcare data sources in Europe: the Clinical Practice Research Datalink (CPRD) Aurum (UK, England and Northern Ireland), the Vaccine Information System (VID) (Valencia region, Spain), Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) (Catalonia region, Spain), and the PHARMO Data Network-GP database (PHARMO) (the Netherlands) (Supplemental Material S1).

2.2. Study population

The study population included subjects who were exposed to the AZD1222 vaccine and 3 comparator cohorts: concurrent unvaccinated subjects (evaluated in all data sources); historical comparators (subjects from 2017 to 2018; evaluated in CPRD, SIDIAP and PHARMO); and mRNA active comparators (vaccinated with a COVID-19 mRNA vaccine; evaluated in CPRD). Subjects were required to have at least 12 months of data available before the index date and complete data on age and sex. Subjects who received AZD1222 as their first COVID-19 vaccine dose were matched to subjects in 3 independent sets of comparator cohorts on age (±2 years), sex, region, prior diagnosis of COVID-19, and status at index date according to codes identifying populations of special interest: (1) receipt of a vaccine against diseases other than COVID-19 within the previous 30 days, (2) pregnancy [6], (3) immunocompromised, (4) autoimmune or inflammatory disorders, or (5) frailty or other relevant comorbidities. The index date for subjects vaccinated with AZD1222 and the matched concurrent unvaccinated subjects was the date when the AZD1222-vaccinated subject received their first AZD1222 dose within the study period. The index date for the historical comparators was the same day and month as that for the matched AZD1222-vaccinated subject but in the year 2017 or 2018. The index date for mRNA active comparators was the date when a subject received their first mRNA COVID-19 vaccine dose within the study period. The matching process is visualised in Fig. 1.

2.3. Follow-up

Subjects were followed up from their index date until the first of the following: end date of the study period; loss to follow-up (e.g., the subject's enrolment termination date in the health plan or system); death; or the end of a predefined 42-day risk window for TTS (see Section 2.4.2). For subjects who received 2 doses of AZD1222 or an mRNA vaccine, a second risk window followed the second dose (Supplemental Fig. S1); for concurrent unvaccinated comparators or historical comparators, a corresponding second risk window was also applied, mirroring the matched vaccinee (Supplemental Fig. S2). Events that occurred during a gap between doses (i.e., outside the risk window) were not included in the study, and follow-up was censored at the time of the event (further details in Supplemental Material S2).

2.4. Variables

2.4.1. Exposure

The exposure of interest was the first vaccination with AZD1222 (i.e., AZD1222 cohort) or with an mRNA COVID-19 vaccine, either Comirnaty

or Spikevax (i.e., mRNA active comparators cohort). Identification of records for AZD1222 and other COVID-19 vaccines varied by data source (Supplemental Material S3). When several COVID-19 vaccination records for a subject occurred close in time, all records within 14 days after the first-ever record of a COVID-19 vaccine were considered as being dose 1, and all records within 90 days after the second and third doses were considered as being doses 2 and 3, respectively. The date of the first record was considered the date of the exposure, and the vaccine formulation (e.g., AZD1222, Comirnaty, Spikevax) was the first non-missing vaccine formulation recorded within 14 days of the exposure date for dose 1 or 90 days for doses 2 and 3. When there was more than 1 vaccination record on the same day, the vaccine formulation was set to "unknown" if the different records had different vaccine formulations. An adaptation of this approach based on expected data reliability was used in PHARMO (Supplemental Material S3).

2.4.2. Outcome

Venous TTS was defined as the novel co-occurrence of a diagnosis of a thromboembolic (TE) event and a diagnosis of thrombocytopaenia (or laboratory evidence of the same, available in CPRD, SIDIAP and PHARMO data sources, i.e., platelet count $<150 \times 10^9$/L) that was made from 10 days before and up to 10 days after the TE event date (definition based on a public multistakeholder VAC4EU webinar) [7] (Supplemental Material S4 lists the *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] codes). Only subjects with a prior history of TTS were excluded, but not those subjects with a history of only one of the subcomponents of TTS (i.e., TE or thrombocytopaenia). The risk window (i.e., time at risk included in the analysis) for venous TTS was 1 to 42 days for each dose, inclusive [8,9]. For each venous TTS event, the date of the earliest of the TE event or thrombocytopaenia was considered the event date. Venous TE events were evaluated overall and by site and included new diagnoses of deep vein thrombosis, splanchnic thrombosis, intracranial or cerebral venous sinus thrombosis (CVST), pulmonary embolism, or other venous thromboembolism. Arterial TE, including myocardial infarction and ischaemic stroke, and other arterial TE were included in the analysis of venous and arterial TTS; this event was also evaluated overall and by site of TE. In addition, a sensitivity analysis using alternative risk windows of 1 to 14 days, 1 to 21 days, and 1 to 28 days, inclusive, after the index date was conducted.

2.4.3. Case validation

For venous TTS events identified in automated data among subjects in the AZD1222 and concurrent unvaccinated cohorts, identification algorithms were validated using manual review of electronic patient profiles (a cumulative, chronologically ordered record of all available electronic linkable information) with blinding of trained clinician adjudicators. Briefly, the Brighton Collaboration case definitions were reviewed and adapted to the study, and REDCap data collection forms were designed and tested using dummy cases. Events were classified according to the Brighton Collaboration case definition level of certainty (LOC); i.e., LOC1 to LOC3 for profiles with enough information to determine a confirmed case, LOC4 for profiles with insufficient information to classify an event as a case or non-case, and LOC5 for profiles classified as a non-case. Positive predictive values (PPVs) were estimated by exposure strata without including LOC4 in the numerator or the denominator (PPV = [LOC1 + LOC2 + LOC3] / [LOC1 + LOC2 + LOC3 + LOC5]) (further details in Supplemental Material S5).

2.4.4. Covariates

Covariates were used to define and describe the study cohorts, populations of special interest, and baseline characteristics or to control

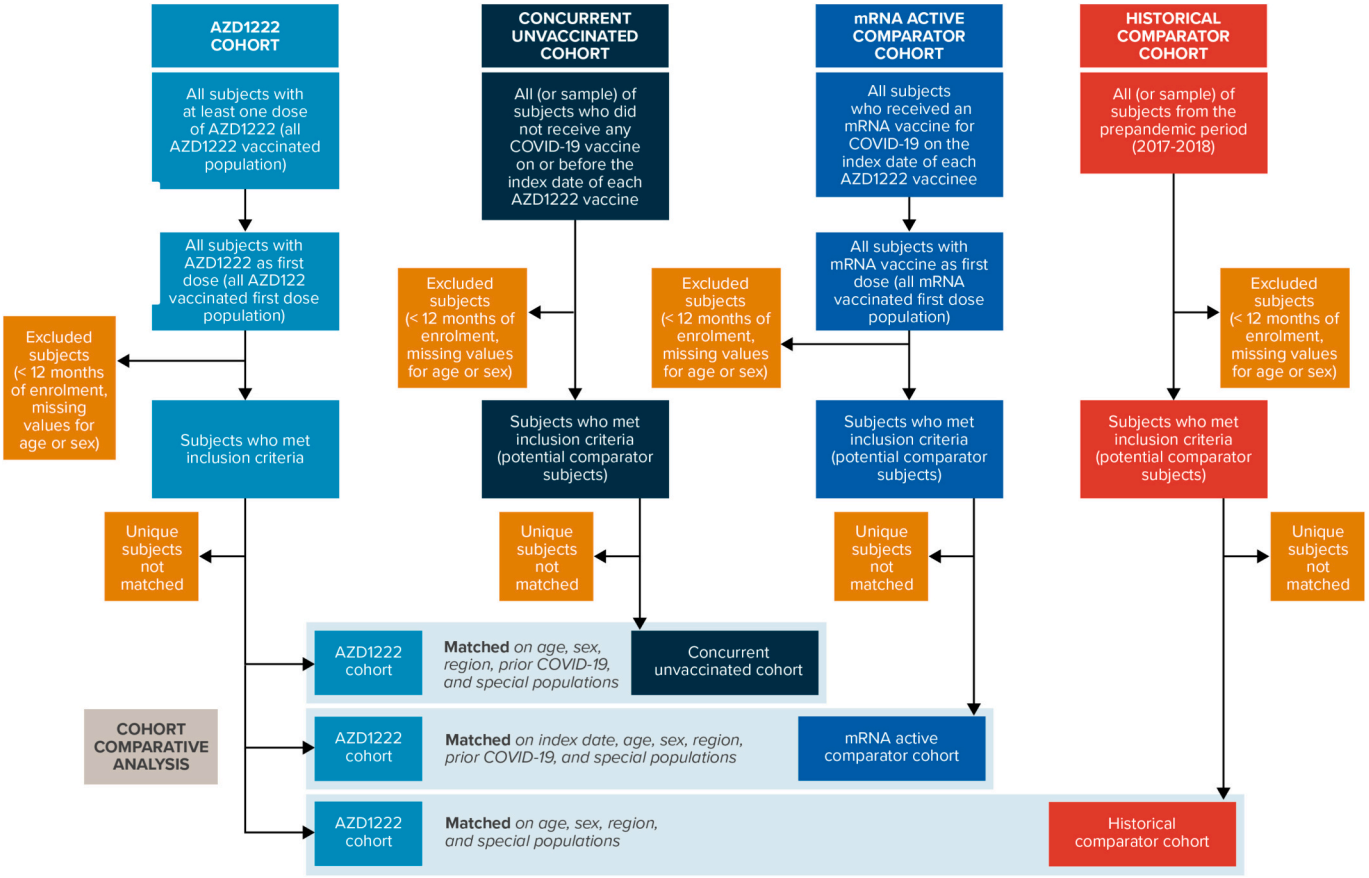

Fig. 1. Assembly of study cohorts.

for confounding (definitions included in Supplemental Material S6). Fig. 2 shows the ascertainment windows for covariates in this study.

2.5. Statistical analyses

The proportion of subjects meeting the eligibility and matching criteria was calculated for each cohort, per data source, followed by the median follow-up (including reasons for censoring) and distribution of matching variables at baseline. For descriptive purposes, cumulative incidence of TTS was estimated using the Kaplan-Meier method from the start of the risk window for the first dose until the end of follow-up, irrespective of the end of the risk window. Adjusted incidence rates (IRs) for TTS (per 10,000 person-years) were estimated in each cohort, and crude and adjusted IR ratios (IRRs) and IR differences (IRDs) were estimated for each comparison, as follows.

Exposure propensity scores (PSs) were estimated with logistic regression (main effects only) at baseline. Baseline confounding was adjusted for by weighting the outcome model with standardised mortality ratio weights, calculated as 1 for subjects in the AZD1222 cohort and PS/(1 − PS) for subjects in the comparator cohort [10]. This approach reweighted the control subjects to be representative of the AZD1222-vaccinated population. Weights were truncated at the 1st and 99th percentiles to reduce variability. Balance between cohorts was assessed before and after weighting using standardised mean differences (SMDs). A covariate was considered imbalanced if the standardised mean difference > 0.10.

After weighting, Poisson regression models with robust estimation (infinitesimal jackknife) of the variance to account for repeated measures were used to obtain adjusted IRs and to estimate unadjusted and adjusted IRRs and IRDs with 95% confidence intervals (CIs) comparing AZD1222 with the 3 matched comparator cohorts. Subjects who received at least 1 dose of AZD1222 were compared with concurrent unvaccinated or historical comparators; subjects who received 2 doses of AZD1222 were compared with subjects who received 2 doses of an mRNA active comparator (Comirnaty or Spikevax as per homologous vaccination regimen). Risk windows following either dose 1 or 2 were included in the estimation of IRs, IRRs, and IRDs; IRs by vaccine dose were estimated in a separate analysis.

Where results from at least 2 data sources were available, random-effects meta-analytic methods were used to estimate pooled crude and adjusted IRRs and 95% CIs [11]. Heterogeneity across data sources was assessed using I^2 [12]. Discussion of the results was not focused on pooled results when the direction of the effect estimates was inconsistent across data sources, or when the estimated I^2 suggested moderate or substantial heterogeneity (i.e., $I^2 > 40\%$) [12]. Cell count restrictions when reporting values <5 were applied in accordance with data source-

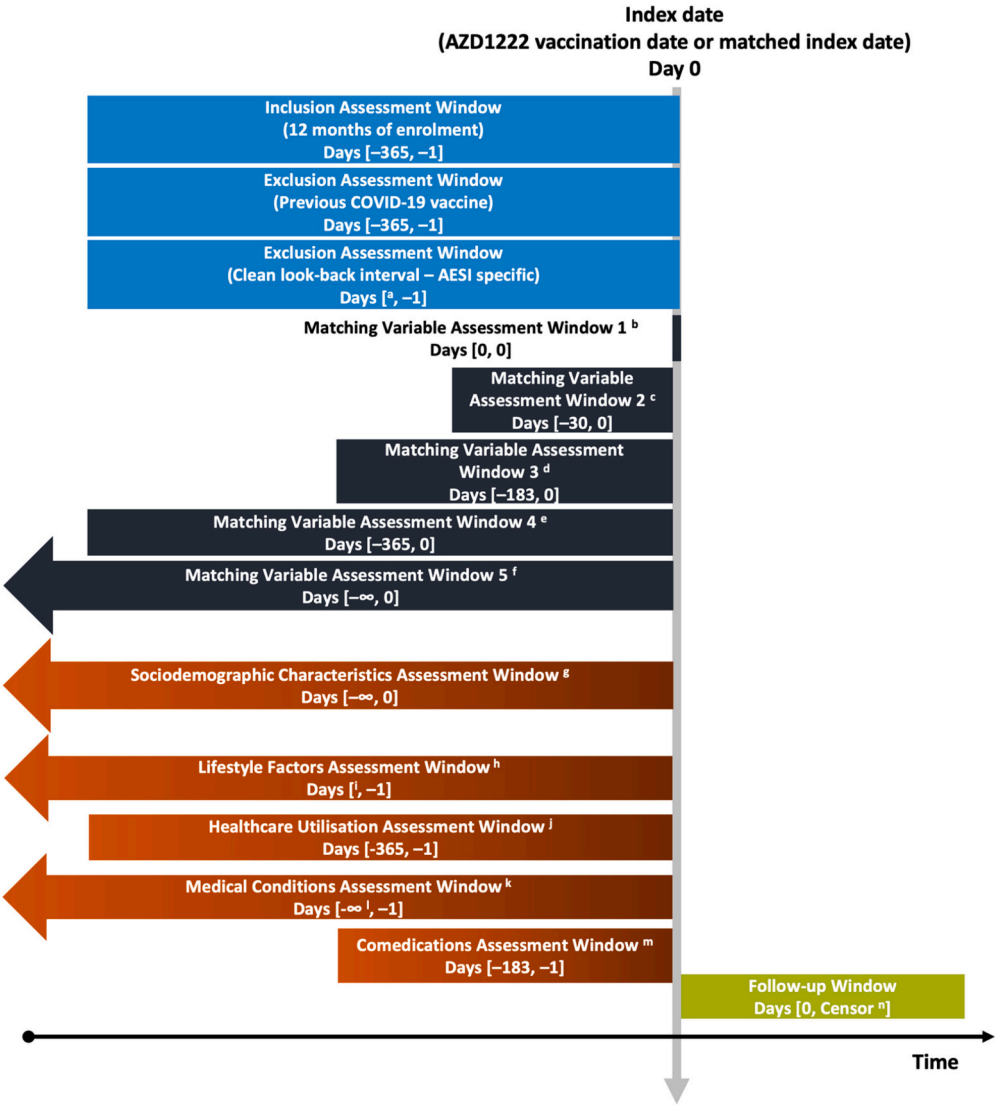

Fig. 2. Summary of covariate ascertainment in cohort analyses.

specific data privacy regulations. Missingness in this study was expected only for some lifestyle or biometric data, such as smoking status or alcohol consumption. If the percentage of subjects with missing values for a specific variable was ≤30%, the variable was included in the PS model with an indicator category for missing values [13]; otherwise, the variable was not included in the PS model and was considered an unmeasured confounder.

For each of the matched cohorts, a number of sensitivity analyses were conducted: (1) censoring both members of a matched pair when either had a COVID-19 diagnosis during follow-up and before the TTS event, to isolate the direct effect of AZD1222 from the effect of COVID-19 (and protection from COVID-19 by vaccination); (2) censoring both members of a matched pair when the unvaccinated subject received a COVID-19 vaccine or the AZD1222 subject received a non-AZD1222 vaccine to estimate the possible selection bias due to informative censoring; (3) use of alternative covariance estimation methods to account for some comparator subjects being matched to multiple AZD1222-vaccinated subjects [14,15]; (4) applying alternative risk windows (1 to 14 days, inclusive, 1 to 21 days, inclusive, and 1 to 28 days, inclusive); (5) analysis of venous and arterial TTS by site; and 6) adjusting the IRRs using the PPV in accordance with Brenner and Gefeller [16]. Subgroup analyses were conducted by age in years (0–11, 12–15, 16–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 or more years) and by special populations of interest.

Additionally, negative control outcome analyses were conducted. Urinary tract infections and nonpathological fractures were used as negative control outcomes for each of the 3 matched cohorts. As described previously, cumulative incidence curves were depicted from the start of the risk window for the first dose until the end of follow-up, irrespective of the end of the risk window.

Lastly, bias analysis [17] was implemented to assess the potential impact of residual confounding due to unmeasured variables or poorly measured variables, such as those for which proxies were used (Supplemental Material S7).

In accordance with the recommendations of the American Statistical Association [18], the International Committee of Medical Journal Editors [19], and expert opinion on the misuse of significance testing [20–22], instead of a dichotomous interpretation based on significance testing, our interpretation considered the magnitude, precision, and potential bias.

3. Results

3.1. Participants and cohort attrition

5,321,930 AZD1222-vaccinated subjects (90.8%) were matched to 5,321,930 concurrent unvaccinated subjects (Table 1). Most subjects who received AZD1222 as their first dose received a second dose of any COVID-19 vaccine, and the most common second-dose vaccine was AZD1222 (ranging from 88.2% in VID to 95.8% in CPRD) (Supplemental Table S1). In all data sources, the median follow-up was longer for the AZD1222 cohort (8.3 to 8.9 months) than for the concurrent unvaccinated cohort (1.0 to 3.2 months) (Supplemental Table S2). The main reason for censoring among the AZD1222 cohort was being vaccinated with a different COVID-19 vaccine; among concurrent unvaccinated subjects, the main reason for censoring was being vaccinated with any COVID-19 vaccine (Supplemental Table S2).

4,831,010 AZD1222-vaccinated subjects (90.3%) were matched to 4,831,010 historical comparators (Supplemental Table S3). Follow-up was longer among the historical comparators (median range, 14.3 months in PHARMO to 14.6 months in SIDIAP) than in the AZD1222 cohort (median range, 8.3 months to 8.9 months) (Supplemental Table S4). Among historical comparators, the main reason for censoring was the matched pair being censored 365 days after their last (first or second) dose of AZD1222 (Supplemental Table S4).

4,028,091 AZD1222-vaccinated subjects (88.3%) were matched to

Table 1
Cohort attrition, matching ratio, and matching distribution for the AZD1222 cohort versus concurrent unvaccinated cohort matched population, by data source.[a, b]

	CPRD Aurum (UK)	VID (Valencia, Spain)	SIDIAP (Catalonia, Spain)	PHARMO (Netherlands)
AZD1222 cohort				
All AZD1222 vaccinated population	4,561,059	508,169	617,054	174,146
All AZD1222 vaccinated first dose population, n (%)	4,546,996 (99.7)	507,356 (99.8)	616,609 (99.9)	167,531 (96.2)
And with no missing data on age and sex	4,546,906 (99.7)	507,356 (99.8)	616,609 (99.9)	167,529 (96.2)
And within the enrolment period[a]	4,333,841 (95.0)	504,926 (99.4)	615,175 (99.7)	167,375 (96.1)
And with at least 12 months look-back period (eligible to be matched)	4,055,814 (88.9)	498,889 (98.2)	611,594 (99.1)	165,763 (95.2)
Unique vaccinated subjects not matched, n (%)	2211 (< 0.1)	185 (< 0.1)	124 (< 0.1)	7610 (4.4)
Unique vaccinated subjects included after matching, n (%)	**4,053,603 (88.9)**	**498,704 (98.1)**	**611,470 (99.1)**	**158,153 (90.8)**
Concurrent unvaccinated cohort				
Unique subjects with no record of vaccination with any COVID-19 vaccine during a period of time within the study period	14,742,803	4,986,567	6,092,192	2,333,502
And with no missing data on age and sex, n (%)	14,742,115 (99.9)	4,986,567 (100)	6,092,192 (100)	2,333,417 (99.9)
And with at least 12 months of look-back time (eligible to be matched), n (%)	12,545,420 (85.1)	4,812,785 (96.5)	5,817,249 (95.5)	2,306,806 (98.4)
Unique unvaccinated subjects matched, n (%)	2,650,525 (18.0)	331,920 (6.7)	426,915 (7.0)	89,233 (3.8)
Unique unvaccinated subjects not matched, n (%)	9,894,895 (67.1)	4,480,865 (89.9)	5,390,334 (88.5)	2,217,573 (95.0)
Non-unique unvaccinated subjects matched[b]	**4,053,603**	**498,704**	**611,470**	**158,153**
Number of times an unvaccinated subject was matched				
Median (Q1, Q3)	1 (1,2)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Min, Max	1, 16	1, 15	1, 11	1, 58
1, n (%)	1,739,334 (65.6)	244,055 (73.5)	305,416 (71.5)	62,351 (69.9)
2, n (%)	583,181 (22.0)	44,892 (13.5)	78,122 (18.3)	12,135 (13.6)

(continued on next page)

Table 1 (*continued*)

	CPRD Aurum (UK)	VID (Valencia, Spain)	SIDIAP (Catalonia, Spain)	PHARMO (Netherlands)
3, n (%)	215,082 (8.1)	22,241 (6.7)	29,111 (6.8)	5765 (6.5)
4, n (%)	76,704 (2.9)	11,455 (3.5)	10,156 (2.4)	3344 (3.7)
5 or more, n (%)	36,224 (1.4)	9277 (2.8)	4110 (1.0)	5638 (6.3)

Q1, first quartile; Q3, third quartile; UK, United Kingdom (England and Northern Ireland only).

Note: For the **AZD1222 cohort**, all percentages are based on the number in the *All AZD1222 vaccinated population*. For the **concurrent unvaccinated cohort**, all percentages are based on the number of "Unique subjects with no record of vaccination with any COVID-19 vaccine during a period of time within the study period." For the number of times an unvaccinated subject was matched, all percentages are based on the number of "Unique unvaccinated subjects matched."

[a] For some subjects, vaccines may have been recorded outside of a period of enrolment in the health plan, or the period of enrolment may have ended on the day of vaccination.

[b] Percentages are not provided because these are non-unique (repeated) subjects.

4,028,091 mRNA-vaccinated active comparators (Supplemental Table S5). Duration of follow-up was similar between AZD1222 and mRNA active comparator cohorts. The main reason for censoring in both cohorts was receipt of a third vaccine dose (Supplemental Table S6).

Baseline distributions of covariates for the matched AZD1222-vaccinated and concurrent unvaccinated cohorts are presented in Table 2. In VID, SIDIAP, and PHARMO, most subjects vaccinated with AZD1222 were aged 60 years or older, and only 45%, 29%, and 21% of the population, respectively, were aged younger than 60 years, whilst in CPRD it was administered to subjects with a wide age range (40–79 years) and 64% were aged younger than 60 years. In CPRD, 83% of AZD1222-vaccinated subjects entered the cohort during the first quarter (Q1) of 2021 (January to March), whereas >60% were vaccinated after Q1 in the other data sources.

Propensity scores overlapped in all data sources and comparisons (Supplemental Fig. S3). The distributions of baseline characteristics were balanced in the weighted populations in all data sources (Supplemental Fig. S4).

3.2. Negative controls

Negative control analyses showed differences in the cumulative incidences from as early as 60 days from index date between AZD1222 and concurrent unvaccinated cohorts in most of the data sources; this was not observed in the negative control analyses for AZD1222 versus mRNA active comparators or for AZD1222 versus historical comparators, except urinary tract infection in SIDIAP (Supplemental Figs. S5-S10).

3.3. TTS events and validation

After validation, resulting PPVs (95% CI) for the AZD1222 cohort ranged between 50.0% (40.2%–59.8%) in VID and 69.2% (60.2%–78.3%) in SIDIAP and, for the concurrent unvaccinated cohort, ranged between 50.0% (40.2%–59.8%) in VID and 84.2% (77.1%–91.4%) in CPRD (Supplemental Material Table S7).

3.4. AZD1222-vaccinated cohort compared with the concurrent unvaccinated cohort

In the primary analysis comparing subjects vaccinated with AZD1222 with concurrent unvaccinated subjects, the adjusted IRRs (95% CIs) for venous TTS (Fig. 3) ranged between 0.34 (0.10–1.18) in VID and 1.14 (0.60–2.17) in CPRD. In PHARMO, no events were captured. The meta-analysis resulted in an IRR of 0.75 (95% CI, 0.42–1.33) with an I^2 of 38.4% and inconsistent direction of effect estimates across data sources. The magnitude of the adjusted IRDs (95% CIs) per 10,000 person-years ranged from −1.16 (−2.90 to 0.58) events in VID to 0.09 (−0.32 to 0.49) events in CPRD (Fig. 3). The adjusted IRR for venous and arterial TTS (Fig. 4) ranged between 0.63 (0.31–1.26) in SIDIAP and 1.21 (0.73–2.01) in CPRD.

Results of the sensitivity analysis for venous TTS showed that in all data sources, the estimated IR and IRR for TTS, where available, were higher in the AZD1222 cohort than in the concurrent unvaccinated cohort in people aged <60 years. In CPRD, VID, and SIDIAP, where estimated, the number of events and the IRs of venous TTS were higher among subjects vaccinated with AZD1222 than among concurrent unvaccinated subjects at all venous thrombosis sites including CVST, splanchnic, and deep vein thrombosis. In CPRD, when the risk window was 1 to 14 days, the IRR (95% CI) of venous TTS was 1.41 (0.52–3.82) and, when the risk window was 1 to 21 days, the IRR was 1.45 (0.63–3.34). In VID and SIDIAP, the adjusted IRRs remained below 1 with shorter risk windows. Analysis correcting the IRRs by PPVs showed that in CPRD, the adjusted IRR (95% CI) decreased from 1.14 (0.60–2.17) in the main analysis to 0.81 (0.40–1.67); in VID and SIDIAP, results were similar to those of the main analysis (Fig. 5 and Supplemental Fig. S13). Sensitivity analysis for venous and arterial TTS were similar to those observed for venous TTS (Supplemental Fig. S14).

3.5. AZD1222-vaccinated cohort compared with the historical and mRNA-vaccinated cohorts

For the exploratory historical comparators analysis, meta-analysis suggested that there was no heterogeneity (I^2 = 0.0% for venous TTS and for venous and arterial TTS), with consistent direction of the effect estimates (Figs. 3 and 4). The IRR (95% CI) of the meta-analysis for venous TTS was 1.78 (1.12–2.82) and for venous and arterial TTS it was 1.30 (0.94–1.80). For the exploratory analysis comparing AZD1222 and mRNA active comparators, the IRR (95% CI) was 1.12 (0.61–2.05) for venous TTS and 1.38 (0.83–2.29) for venous and arterial TTS (Figs. 3 and 4). No additional trends were identified in the exploratory sensitivity and subgroup analyses (Supplemental Figs. S15–18).

3.6. Bias analysis

With an observed IRR of 1.14, bias analysis indicated that an unmeasured confounder would need to have an association with TTS of IRR ≤0.5 or ≥ 2 and an approximately ≥20% absolute difference in prevalence between the AZD1222 and concurrent unvaccinated cohorts to lead to an IRR of 1 after bias adjustment (Supplemental Fig. S19).

4. Discussion

The current study is one of the largest observational comparative studies evaluating the safety of the AZD1222 vaccine to date, examining the risk of TTS among more than 5 million subjects vaccinated with AZD1222 across 4 data sources in 3 European countries. The study compared the subjects vaccinated with AZD1222 with concurrent unvaccinated subjects, historical comparators from a pre–COVID-19 pandemic period (2017–2018), and concurrent subjects vaccinated with mRNA COVID-19 vaccines. Each of these comparisons attempted to answer different, but closely related, research questions and to address different limitations.

The higher risk of TTS observed in the current study among AZD1222-vaccinated subjects within younger age groups, and when using shorter risk windows, is in keeping with other observational studies conducted in England [23,24]. In the cohort study conducted by Andrews et al. [23] which used National Health Service vaccination data and electronic health records, the relative incidence (RI) (95% CI) of venous TTS among the age groups 15 to 39 years, 40 to 64 years, and 65

Table 2
Distribution of baseline matching characteristics among the matched population for the analysis between AZD1222 and concurrent unvaccinated comparators, by data source.[a]

	CPRD Aurum (UK)		VID (Valencia, Spain)		SIDIAP (Catalonia, Spain)		PHARMO (Netherlands)	
	AZD1222 cohort	Unvaccinated cohort	AZD1222 cohort	Unvaccinated cohort	AZD1222 cohort	Unvaccinated cohort	AZD1222 cohort	Unvaccinated cohort
Total subjects	**4,053,603**	**4,053,603**	**498,704**	**498,704**	**611,470**	**611,470**	**158,153**	**158,153**
Calendar quarter at the index date								
Q4 2020[a]	< 0.1%	< 0.1%	0%	0%	0%	0%	0%	0%
Q1 2021	83.0%	83.0%	36.5%	36.5%	38.3%	38.3%	39.7%	39.7%
Q2 2021	16.3%	16.3%	62.2%	62.2%	61.4%	61.4%	59.4%	59.4%
Q3 2021	0.5%	0.5%	1.3%	1.3%	0.2%	0.2%	0.8%	0.8%
Q4 2021	0.1%	0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Q1 2022	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Q2 2022	0%	0%	0%	0%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Age at the index date, mean (SD), years	54.5 (14.6)	54.5 (14.6)	53.8 (12.0)	53.8 (12.0)	57.9 (11.7)	57.9 (11.7)	58.7 (10.1)	58.7 (10.1)
Age group, years								
0–11	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
12–15	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
16–19	0.7%	0.7%	0.4%	0.4%	0.3%	0.3%	0.7%	0.7%
20–29	4.6%	4.6%	6.2%	6.2%	4.4%	4.4%	3.1%	3.1%
30–39	8.4%	8.4%	9.2%	9.2%	6.1%	6.1%	3.3%	3.3%
40–49	22.7%	22.7%	13.3%	13.3%	8.8%	8.8%	5.0%	5.0%
50–59	27.7%	27.7%	16.3%	16.6%	9.6%	10.1%	9.0%	11.9%
60–64	10.9%	10.9%	51.3%	50.8%	39.5%	39.0%	70.9%	65.2%
65–69	8.5%	8.5%	3.3%	3.4%	31.1%	31.1%	6.0%	8.7%
70–74	8.1%	8.1%	0.1%	0.1%	0.1%	0.1%	0.8%	0.8%
75–79	4.7%	4.7%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	0.3%	0.3%
80–84	1.7%	1.7%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	0.3%	0.3%
85 or older	2.0%	2.0%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	0.6%	0.6%
Sex, female	51.1%	51.1%	56.0%	56.0%	54.5%	54.5%	53.2%	53.2%
Duration of look-back period (years), mean (SD)	15.4 (9.1)	14.7 (9.1)	3.3 (0.2)	3.3 (0.2)	7.2 (0.7)*	7.0 (1.0)*	10.5 (1.8)	10.3 (2.1)
COVID-19 history (positive antigen or PCR test or diagnosis)	6.5%	6.5%	6.1%	6.1%	5.8%	5.8%	2.7%	2.7%
Recent history of vaccination with non–COVID-19 vaccines within 30 days before or at the index date	0.8%	0.8%	< 0.1%	< 0.1%	0.1%	0.1%	0.0%	0.0%
Pregnant at the index date	0.1%	0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Immunocompromised	8.9%	8.9%	5.4%	5.4%	4.4%	4.4%	4.8%	4.8%
Autoimmune or inflammatory disorders	8.4%	8.4%	4.7%	4.7%	3.5%	3.5%	4.1%	4.1%
Frailty or other relevant comorbidities	25.8%	25.8%	20.1%	20.1%	22.2%	22.2%	15.4%	15.4%
Subjects with at least 1 indicator of frailty within 1 year before the index date	3.0%	2.8%	3.3%	3.3%	1.6%	1.7%	1.7%	1.6%
At least 1 other relevant comorbidity	24.8%	24.7%	17.9%	18.1%	21.1%	21.2%	14.2%	14.2%

PCR, polymerase chain reaction; Q*n* yyyy, quarter of the calendar year; SD, standard deviation; UK, United Kingdom (England and Northern Ireland only).

[a] In CPRD Aurum, 87 subjects in each cohort entered the study period in Q4 2020.

* Standardised mean difference > 0.1.

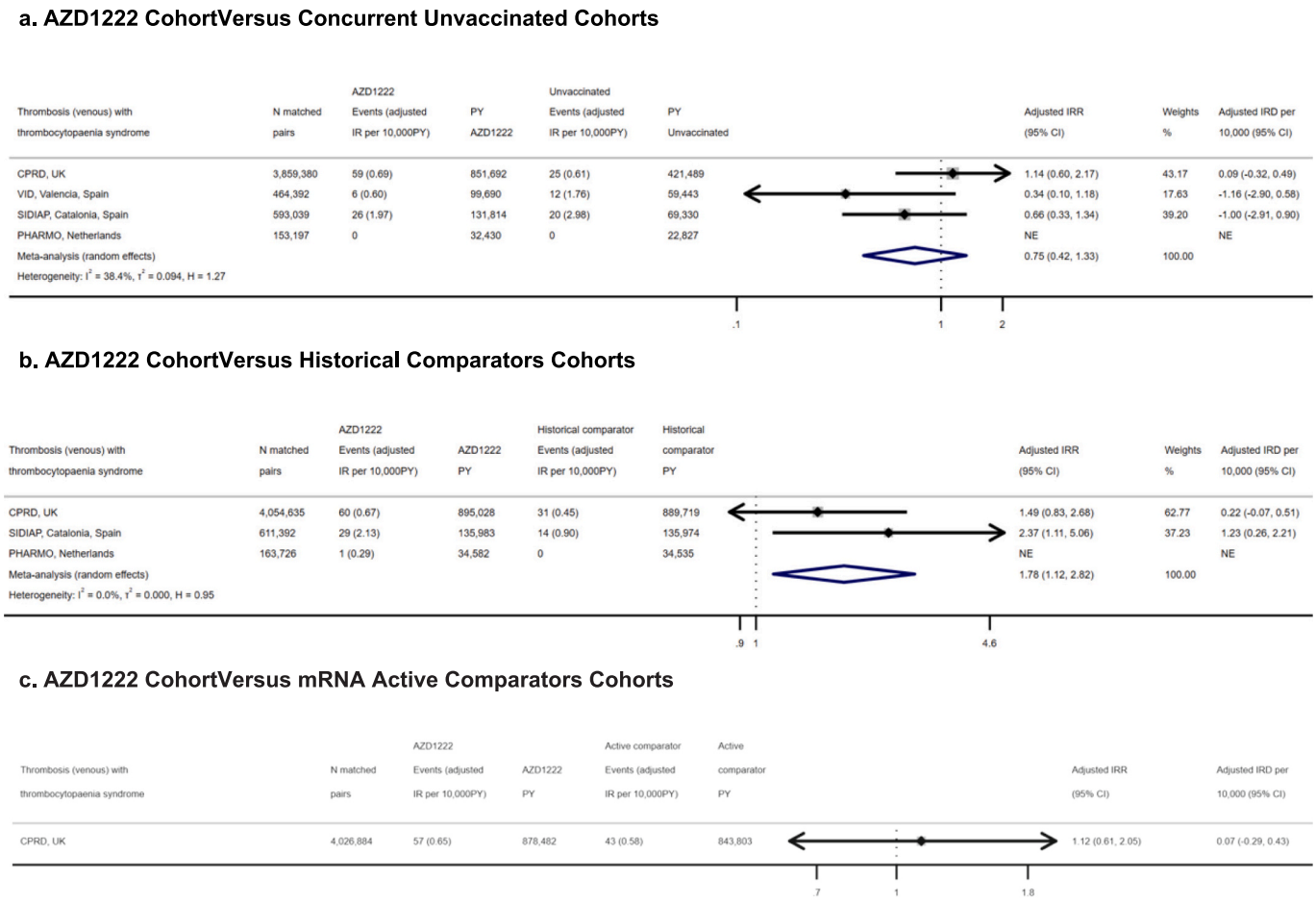

Fig. 3. Adjusted IRs, IRRs, and IRDs for venous TTS (Risk Window: 1 to 42 Days) after weighting in the matched population, by cohort comparison and data source.

years or older was 38.2 (17.6–82.9), 5.4 (3.0–9.7), and 2.1 (1.0–4.5), respectively, during the 4 to 13 days after vaccination and 22.1 (9.3–52.5), 5.2 (2.9–9.3), and 1.7 (0.8–3.7), respectively, during the 14 to 27 days after vaccination. In the self-controlled case series conducted by Higgins et al. [24] which used electronic health records from 4 hospitals, the RI of venous and arterial TTS events among subjects vaccinated with AZD1222 compared with the pre-vaccination baseline period was also higher when using shorter risk windows and higher among subjects aged 18 to 39 years (RI = 5.61 [95% CI, 0.92–34.35] in the 4 to 13 days after vaccination, and RI = 3.45 [95% CI, 0.39–30.61] in the 14 to 27 days after vaccination) than among subjects aged 40 to 64 years (RI = 1.60 [95% CI, 0.51–5.05] in the 4 to 13 days after vaccination, and RI = 0.99 [95% CI, 0.26–3.71] in the 14 to 27 days after vaccination) or aged 65 or more years (RI = 1.24 [95% CI, 0.39–3.93] in the 4 to 13 days after vaccination, and RI = 1.28 [95% CI, 0.43–3.80] in the 14 to 27 days after vaccination).

The observed higher frequency of venous TTS after the first dose of AZD1222 compared with the second dose observed in the current study was also observed in the UK cohort study by Li et al. [25]. In addition, the European Medicines Agency requested the Early COVID-Vaccine Monitoring (ECVM) study that was conducted in 3 data sources; CPRD Aurum (UK), Agenzia Regionale di Sanità (Italy), and BIFAP (Spain). No events after the second dose of AZD1222 were reported in the ECVM study, although this could be partially explained by the study period, which ended in October 2021, when the rollout of second doses was not finalised [26].

The potential increased risks of venous TTS and venous and arterial TTS observed in our study when comparing AZD1222 and historical comparators cohorts are in line with the increased risks reported in the literature in studies comparing study and background rates or estimating observed/expected ratios [26–28]. In the ECVM study conducted from January 2020 to October 2021, during the 28 days after vaccination with a first or second dose of AZD1222, the pooled IRR of venous and arterial TTS across data from CPRD Aurum (UK), ARS (Italy), and BIFAP (Spain) was 2.98 (95% CI, 1.67–5.31) [26]. The standardised incidence ratio (SIR) (i.e., observed vs expected events ratio) of venous TTS was increased in the studies performed by Observational Health Data Sciences and Informatics in CPRD Aurum during September 2020 to May 2021 (SIR = 1.38; 95% CI, 0.85–2.26) [27] and in SIDIAP during December 2020 to June 2021 (SIR = 1.28; 95% CI, 0.64–2.56) [28]. Finally, in the current study, the IRR of 1.38 (95% CI, 0.83–2.29) for venous and arterial TTS observed in CPRD in subjects vaccinated with AZD1222 compared with subjects vaccinated with mRNA vaccines is similar to the IRR of 1.29 (95% CI, 0.94–1.77) reported in a cohort study of subjects vaccinated with a first dose of AZD1222 compared with subjects vaccinated with a first dose of Comirnaty in the UK [25].

No studies have reported decreased risks of TTS among vaccinated subjects with AZD1222; thus, the findings from the main analysis in VID and SIDIAP should be interpreted with caution. These findings are likely to be explained by the differences in age distributions of these populations, since IRs for TTS in CPRD and in the literature were higher among age groups younger than those age groups most frequently vaccinated with AZD1222 in VID, SIDIAP, and PHARMO. The age distribution of vaccinees in these data sources is in line with the age restrictions applied in each country, which occurred earlier in Spain and the Netherlands than in the UK and were more restrictive (starting in late March 2021 and restricted to subjects aged 60–69 years in Spain and 60–75 years in the Netherlands, whilst the UK was restricted to subjects

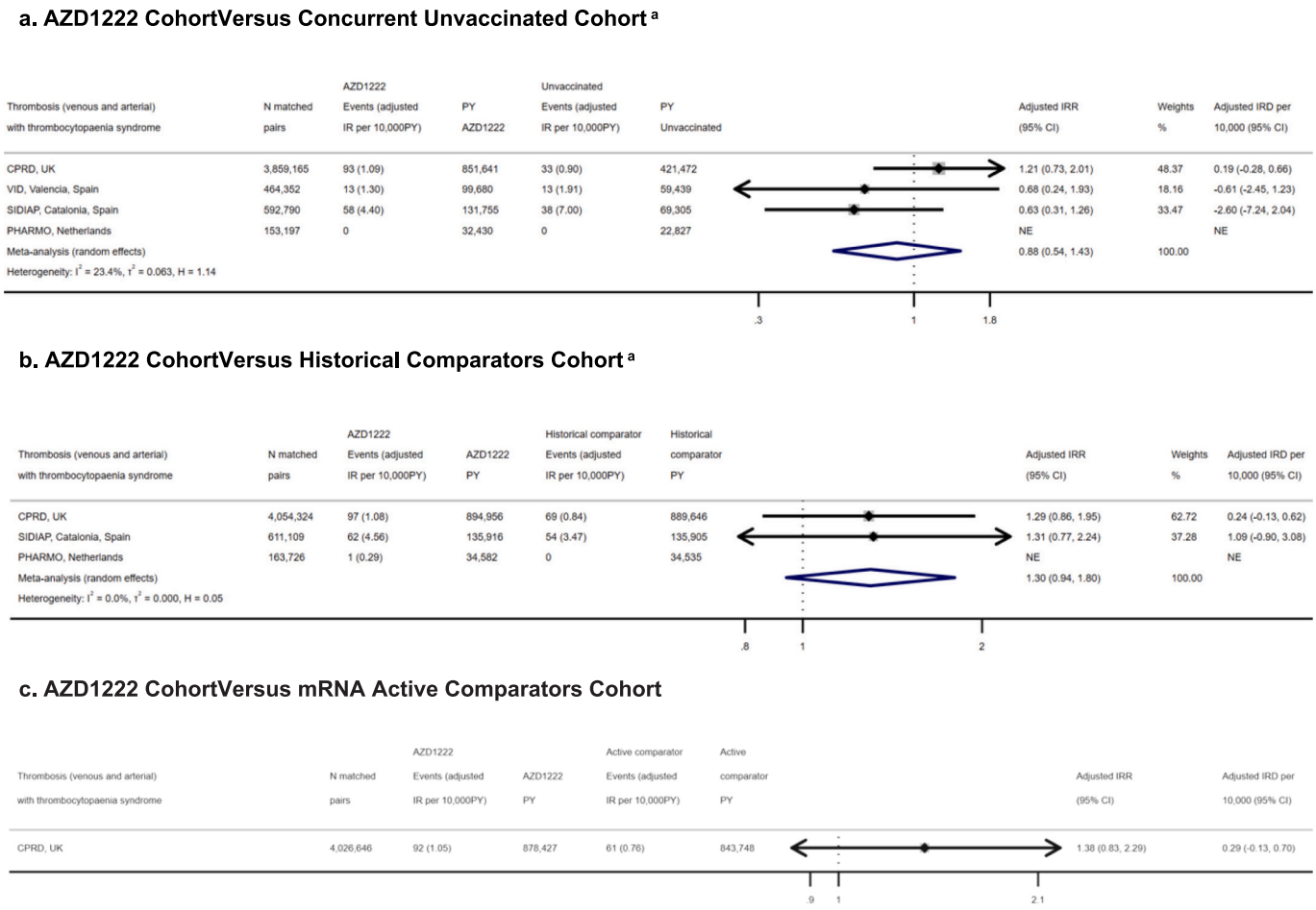

Fig. 4. Adjusted IRs, IRRs, and IRDs for venous and arterial TTS (Risk Window: 1 to 42 Days) after weighting in the matched population, by cohort comparison and data source.

older than 30 years in April 2021 and to subjects older than 40 years in May 2021).

The IRR of TTS restricted to CVST could not be evaluated in any data source due to the low number of events. However, higher IRs of TTS restricted to CVST were observed in the AZD1222 cohort than in the concurrent unvaccinated cohort across data sources with events. These results are in line with the initial case reports that gave rise to the TTS signal of thrombosis in unusual sites, such as CVST, [29,30], and they are in line with background rates studies [7,31]. In addition, a population-based register study in Finland [32] reported a crude IR for TTS restricted to CVST of 12.1 per million person-years within the 28 days after vaccination with AZD1222, which was 67 times higher than the background rate and resulted in an IRR of 40 (95% credible interval, 6–161) after adjusting for age and sex.

Findings from the negative control analyses suggested that the results of the analysis comparing AZD1222-vaccinated subjects with concurrent unvaccinated subjects were likely affected by selection bias due to informative censoring among concurrent unvaccinated subjects (due to high rates of vaccination with COVID-19 vaccines), which limits the interpretation of the comparative primary analysis. Although a large validation effort was conducted in a standardised manner, outcome misclassification was a potential source of bias. The PPV-adjusted IRRs were below 1 in all data sources. However, results of the validation and subsequent sensitivity analyses should be interpreted with regard to the limitations encountered. First, the total number of events was low, leading to limited precision of the PPV estimates. Second, the high proportion of events classified as non-evaluable (LOC4) due to limited availability of data, such as laboratory and imaging results, highlighted the complexities of identifying TTS in secondary data sources when relying on algorithmic definitions. However, availability of data varied by data source: e.g., in VID, additional hospital data could be requested for all subjects, and in SIDIAP, additional hospital data could be requested for 40% of the hospitals. Third, a lower proportion of events were classified as a non-case (LOC5) most frequently due to preexisting thrombocytopaenia or thrombosis prior to vaccination. This was the consequence of only excluding subjects that fulfilled the definition of TTS, which was considered a distinct clinical entity, before the index date. Another potential limitation that may have affected the comparability of the study cohorts was residual confounding. Although subjects vaccinated with AZD1222 and concurrent unvaccinated subjects were matched on several characteristics at baseline, the decision to remain unvaccinated regardless of vaccination policies may have been related to lifestyle choices or healthcare-seeking behaviours, which are difficult to capture in electronic data sources. Quantitative bias analysis showed that if there were small differences in the distribution of an unmeasured confounder between cohorts coupled with a moderate magnitude of the association between the unmeasured confounder and the outcome, the estimated relative risks that were closer to 1 (e.g., venous TTS IRR = 0.66 in SIDIAP or 1.14 in CPRD) could be partially explained by residual confounding.

AZD1222-vaccinated subjects and historical comparators may not have been entirely comparable, since reporting and recording of TTS or its components may have changed during the pandemic. This should not be the case for the comparisons between AZD1222-vaccinated subjects and mRNA active comparators, and it is unlikely that these comparisons were affected by selection bias due to informative censoring.

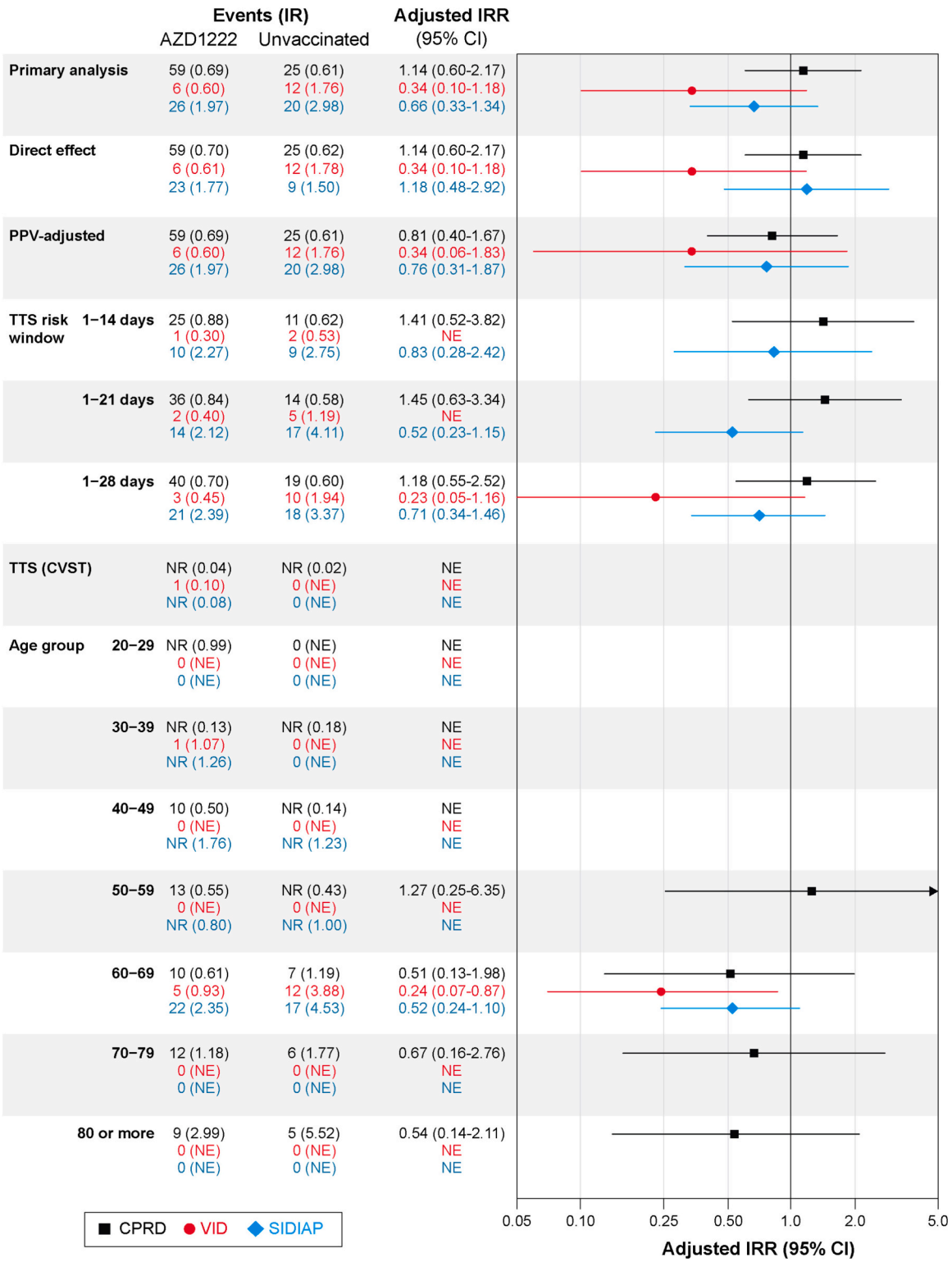

Fig. 5. Subgroup and sensitivity analyses for the comparison between AZD1222 and concurrent unvaccinated cohorts, by data source, for venous TTS (Risk Window: 1 to 42 Days).

While TTS is recognised as a vaccine-triggered autoimmune process, the host-specific factors that permit this breach of tolerance remain undefined [33–36]. These host-specific factors may relate to transient alterations in regulatory networks, prior immune priming, or a person's immunogenetic background [36,37]. While younger females have a higher frequency of autoimmune conditions [38], and an initial trend toward a higher occurrence of TTS after vaccination with AZD1222 among younger females was observed [39], later publications suggested that the initial female over-representation likely reflected early rollout demographics [40,41]. Similarly, no consistent higher risk of TTS has been reported among patients with preexisting autoimmune disease. In this study, evaluation of the risk of TTS among women of childbearing age was not part of the study objectives and could not be explored due to the low number of events (i.e., across all data sources, there were 10

subjects or fewer for all age-group strata below 50 years), that did not allow the conduct of further subgroup analysis by age and sex. Also in this study, results suggested a decreased risk of TTS among patients with autoimmune conditions, although this was based on a low number of events (Supplemental Fig. S13).

5. Conclusions

Considering the magnitude, precision, and potential biases—such as selection bias due to informative censoring among concurrent unvaccinated participants, or potential outcome misclassification—the totality of evidence suggests a possible increased risk of TTS post AZD1222 vaccination that may be higher among subjects aged <60 years and in the 1–42 days after a first-dose vaccination with AZD1222. Differential age distributions, resulting from country-level differences in the risk minimisation measures, may explain IRR disparities across data sources.

CRediT authorship contribution statement

Joan Forns: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Romin Pajouheshnia:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Taylor Aurelius:** Writing – review & editing, Validation, Conceptualization. **Zachary Bouck:** Writing – review & editing, Methodology, Conceptualization. **Juan José Carreras:** Writing – review & editing, Validation, Methodology, Conceptualization. **Jungyeon Choi:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Albert Cid Royo:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Elisa Correcher-Martínez:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Silvia Fernandez-Garcia:** Writing – review & editing, Validation, Conceptualization. **Catherine Fry:** Writing – review & editing, Methodology, Conceptualization. **Jordy Gaspersz:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Maria Giner-Soriano:** Writing – review & editing, Methodology, Conceptualization. **Rosa Gini:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Anna Girardi:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Ron Herings:** Writing – review & editing, Conceptualization. **Wan-Ting Huang:** Writing – review & editing, Methodology, Conceptualization. **Giulia Hyeraci:** Writing – review & editing, Methodology, Conceptualization. **Joseph Kim:** Writing – review & editing, Methodology, Conceptualization. **Samantha Lane:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Deborah Layton:** Writing – review & editing, Methodology, Conceptualization. **Andrew Lee:** Writing – review & editing, Methodology, Conceptualization. **Thom Lysen:** Writing – review & editing, Methodology, Conceptualization. **David Martinez:** Writing – review & editing, Visualization, Formal analysis, Data curation, Conceptualization. **Sima Mohammadi:** Writing – review & editing, Validation, Conceptualization. **Denise Morris:** Conceptualization. **Rosa Morros:** Writing – review & editing, Validation, Methodology, Conceptualization. **Dan Ouchi:** Writing – review & editing, Visualization, Formal analysis, Data curation, Conceptualization. **Jetty Overbeek:** Writing – review & editing, Methodology, Conceptualization. **Susana Perez-Gutthann:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Estel Plana:** Writing – review & editing, Validation, Formal analysis, Data curation, Conceptualization. **Robert W. Platt:** Writing – review & editing, Methodology, Conceptualization. **Giuseppe Roberto:** Writing – review & editing, Methodology, Conceptualization. **Debabrata Roy:** Writing – review & editing, Methodology, Conceptualization. **Miriam C.J. Sturkenboom:** Writing – review & editing, Methodology, Conceptualization. **Amirreza Dehghan Tarazjani:** Writing – review & editing, Validation, Conceptualization. **Hae-Won Uh:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Arantxa Urchueguía-Fornes:** Writing – review & editing, Methodology, Conceptualization. **Daniel Weibel:** Writing – review & editing, Methodology, Conceptualization. **Cristina Rebordosa:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JF, RP, EP, DM, SPG, and CR are employees of RTI Health Solutions which is a unit of RTI International, a nonprofit organization that conducts work for government, public, and private organizations, including pharmaceutical companies.

MS, ACR, HWU, JC, DW are employees of the University Medical Center Utrecht, which is a not-for-profit academic teaching hospital, which conducts studies for public and private organizations, including pharmaceutical companies.

ZB and JK are employees of, and may or may not hold stock in, AstraZeneca.

AL is an employee of, and receives salary from, Source Group Limited, but their work is contracted out to AstraZeneca and they may or may not hold stock in AstraZeneca.

During the conduct of this study, DL was an employee of and received a salary from PEPI Consultancy Ltd. and received funds from AstraZeneca Ltd., Ariello SRO and Annexon Biosciences Inc. DL is now an employed as Drug Safety Lead at Lane Clark and Peacock (LCP) LLP, UK.

JAO, TSL, JG, and RMCH are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

DR, SL, DM, CF and TA are employees of the Drug Safety Research Unit (DSRU). The DSRU is an independent charity (No 327206) which works in association with the University of Portsmouth.

DO, MGS, SFG and RM are employees of IDIAPJGol. They are working on other projects funded by pharmaceutical companies in the institution, which are not related to this study and with no personal profit.

AUF, JJCM and ECM are employees of the Vaccine Research Department (VRD) at FISABIO. The research group performs financially supported studies for government, other related healthcare authorities and several pharmaceutical companies. AUF and ECM are working on other projects, not related to this study, funded by pharmaceutical companies.

RG is employed and GR, GH and AG are consultants of Agenzia Regionale di Sanità (ARS Toscana), a research centre owned by the Tuscany Region. The budget of ARS Toscana is partially supported by studies funded by public institutions and private companies and compliant with the ENCePP Code of Conduct. ARS Toscana is a member of VAC4EU.

RWP has received funds for consulting from Merck, Pfizer, and Biogen, outside the scope of this work.

WTH is a scientific advisory board member of VAC4EU; no other disclosures relevant to this submitted work were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128723.

Data availability

The data that has been used is confidential.

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