Association between COVID-19 Vaccination (ChAdOx1-S) and Thromboembolic, Thrombocytopenic, Hemorrhagic Events: A Systematic Review and Meta-analysis of Analytical Epidemiological Studies

Raman S. Vaman*, Muthusamy S. Kumar*[1], Kathiresan Jeyashree[2], Ashok Periasami, Rizwan S. Abdulkader[3], Manoj Murhekar[4]

Scholar, [1]Scientist C, [2]Scientist E, [3]Scientist D, [4]Scientist G, ICMR-School of Public Health, ICMR- National Institute of Epidemiology, Chennai, Tamil Nadu, India
*Equal contribution.

Abstract

We conducted a systematic review of analytical epidemiological studies to assess the association between ChAdOx1-S vaccination and thromboembolic, thrombocytopenic, and hemorrhagic events. We searched Medline, Embase, Google Scholar, WHO-COVID-19 database, and medRxiv for studies evaluating the association between ChAdOx1-S and vascular events. Primary outcomes of interest were cerebral venous sinus thrombosis, peripheral venous thrombosis (PVT), and thrombocytopenia. Two independent reviewers screened for eligible studies, extracted data, and assessed the risk of bias. The DerSimonian-Laird random effects model was used to pool the incidence rate ratios (IRRs) separately for the first and second doses. Heterogeneity was assessed using I^2 statistics. Twenty studies were included, of which 11 were self-controlled case series, and nine were cohort studies (254 million participants). Pooling of 17 studies showed a higher risk of cerebrovascular thrombosis (IRR = 3.5, 95% CI = 2.2–5.4, I^2 = 79%), PVT (IRR = 2.0, 95% CI = 1.1–3.5, I^2 = 95%) and thrombocytopenia (IRR = 1.6, 95% CI = 1.4–1.9, I^2 = 93%) among those who received ChAdOx1-S vaccination as compared to controls. No increased risk was seen after the second dose or for secondary outcomes. There is moderate-to-high certainty of the evidence for the increased risk of cerebral venous sinus thrombosis, PVT, and thrombocytopenia following the first dose of the ChAdOx1-S vaccine.

Systematic Review Registration: PROSPERO CRD42022372768.

Keywords: Adverse events following immunization, ChAdOx1-S, COVID-19 vaccines, thrombocytopenia, venous thrombosis

INTRODUCTION

The global COVID-19 vaccination strategy aims to reduce deaths and severe disease, protect health systems, and resume socioeconomic activities by vaccinating high- to low-priority groups sequentially.[1] As of February 16, 2023, 13.2 billion vaccine doses were administered globally. However, the coverage remains low globally, with 64.9% for the primary series and 30.7% for a booster dose.[2] Of the 13 vaccines approved by the World Health Organization (WHO) for emergency use, four were recombinant, adenoviral vectored. ChAdOx1-S (AstraZeneca COVID-19 vaccine AZD1222 Vaxzevria™, SII COVISHIELD™) is an adenoviral vectored vaccine recommended in a two-dose schedule with an interval of 4–12 weeks.[3]

During early 2021, cases of venous thrombosis with thrombocytopenia were reported within 3–4 weeks of vaccination with ChAdOx1-S.[4,5] Following these reports,

Access this article online

Quick Response Code:

Website:
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DOI:
10.4103/ijcm.ijcm_676_23

several European countries briefly stopped using ChAdOx1-S.[6] European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee reviewed venous thrombosis cases reported to EudraVigilance, the EU drug safety database. The committee recommended listing thrombosis with thrombocytopenia syndrome (TTS), cerebrovascular and sinus thrombosis, and thrombocytopenia as very rare side effects of ChAdOx1-S in the product information brochure. EMA concluded that the benefits of receiving this vaccine by preventing COVID-19 hospitalizations and deaths outweigh the risks.[7] The WHO's interim recommendations on ChAdOx1-S listed TTS as a rare adverse event.[3]

Several case reports and case series were published on thromboembolic events during the scale-up of COVID-19 vaccination.[4,5,8] To date, 10 systematic reviews have described the clinical features and outcomes of the thromboembolic events following adenoviral COVID-19 vaccines (***Supplementary Appendix***). These reviews found that most thromboembolic events were reported after vaccination with ChAdOx1 or Ad26.COV2. The most common events were cerebral venous sinus thrombosis, deep vein thrombosis, and pulmonary embolism. The frequency of these events was higher among females and younger adults. Symptoms usually appeared 1–2 weeks after vaccination, with a mortality rate of 16%–39% (***Supplementary Appendix***). However, none of these reviews was able to provide any epidemiological measure of the strength of association necessary for causal inference because they were all based on case reports/series.

Although case reports and case series are instrumental in generating a hypothesis of a possible association between the adenoviral vectored COVID-19 vaccine and thromboembolic events, they have limited value in establishing a causal linkage. Epidemiological studies such as case-control, cohort, clinical trials, and self-controlled case series are more appropriate for such causal questions. Therefore, we conducted a systematic review and meta-analysis of analytical studies to determine the strength of the association between ChAdOx1-S vaccination and the incidence of thromboembolic, thrombocytopenic, and hemorrhagic events.

METHODS

We registered this review in PROSPERO (CRD42022372768) and reported its findings per the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines.[9]

Study selection

We included case-control studies, cohort studies, self-controlled case series, and randomized controlled trials in this review. The study population in the included studies were all those who were eligible for receiving the COVID-19 vaccine at those particular time points. Our exposure of interest was one or two doses of the ChAdOx1-S vaccine. The control groups comprised either pre-vaccinated or unvaccinated individuals or recipients of other COVID/non-COVID vaccines. We excluded

single-group cohorts without a comparison group, case reports, editorials, opinions, letters, and studies done exclusively on children. We grouped studies depending on the dose number of the ChAdOx1-S vaccine. We did not apply any language or time restrictions. More details of the study eligibility criteria can be found in the supplement (***Supplementary Appendix***).

Information sources and study selection

We searched for eligible studies in Medline (via PubMed), Embase, Google Scholar, the WHO-COVID-19 research database, and medRxiv. In addition, the reference list of all included articles was searched for any additional studies. The search was last performed on November 27, 2022. Details on the search strategy are given in the supplement (***Supplementary Appendix***). Two independent reviewers (MSK and RSV) conducted the study screening and selection independently using the pre-specified inclusion and exclusion criteria. These reviewers were blinded to each other's decisions. A third reviewer (SAR) resolved any conflicts in the study selection. We used *Rayyan* (a web application to manage literature) to conduct the title and abstract screening and full-text inclusion to ensure reproducibility and verification.[10]

Data extraction

We extracted data from the eligible full-text articles by using a pre-tested data abstraction form. Two reviewers independently verified the extracted data for accuracy. We extracted the first author, year of publication, age group of the study population, countries, study design, dose number of the ChAdOx1-S vaccine, comparison group or period, type of outcome, risk period during which the outcome was measured, and the measure of association reported. For the meta-analysis, we extracted the author-reported measures of association, which included odds ratio, relative risk, risk difference, incidence rate ratio (IRR), incidence rate difference, hazard ratio, or standardized mortality ratio (SMR). We also extracted the 95% confidence interval (95% CI) for all measures.

Outcomes

Our primary outcomes of interest were central venous thrombosis (CVT), peripheral venous thrombosis (PVT), and thrombocytopenia. Our secondary outcomes of interest were other thrombo-embolic events, such as any type of venous/arterial thromboembolic (VTE/ATE) and hemorrhagic events, myocardial infarction/coronary artery disease (MI/CAD), and stroke.

We included outcomes and risk periods as defined by the individual study authors and did not make any attempts to standardize the diagnostic or clinical criteria across the included studies (***Supplementary Appendix***). All outcomes were extracted within the specific study-defined risk periods (following the first or second dose). If outcomes were available for multiple periods, all were extracted and aggregated later to match the other studies. Similarly, if outcomes were available for multiple age groups, all the effect sizes were extracted and aggregated for pre-defined age groups. If outcomes were reported against multiple comparison groups,

preference was given to pre-vaccinated/unvaccinated first, followed by other types of COVID-19 vaccines and vaccines for other infectious diseases. Within a given study, all available pre-specified outcomes were extracted. We did not attempt to extract outcomes that did not fit our study definitions.

Risk of bias (RoB) assessment

We assessed the risk of bias by using the Newcastle-Ottawa tool for cohort studies and the modified Newcastle-Ottawa tool for self-controlled case series.[11] Details of the tools are given in the supplementary appendix**.** Two reviewers completed the assessment independently, and a third reviewer resolved discrepancies, if any.

Statistical methods

We planned to pool studies reporting similar measures of association. As most of the studies retrieved were cohorts and self-controlled case series, we used IRR as the effect size for the meta-analysis. For studies that did not directly report an IRR, we calculated the IRR and exact 95% CIs by using the method reported by Miettinen from the reported count of cases and person-years of observation.[12] To avoid unit-of-analysis error, we aggregated effect sizes reported across multiple age groups/time points within a study by using standard inverse-variance weighting and assuming an independent structure for the sampling errors. We used the DerSimonian-Laird random effects model to pool the IRRs separately for one-dose and two-dose studies. Pooling was done on the log-transformed IRRs and their 95% CIs and back-transformed for presentation in forest plots. We planned to conduct subgroup analysis for age, type of comparison, and risk periods if sufficient studies were retrieved. We assessed between-study heterogeneity by using I^2 statistics. An I^2 value of > 50% was considered evidence of significant heterogeneity. We assessed small-study effects by plotting the effect size against their standard error in funnel plots and examined them for asymmetry. We planned to conduct formal statistical tests such as Egger's test for publication bias only if there were at least 10 studies per outcome per dose type. We planned to conduct a sensitivity analysis by excluding articles with a high risk of bias. All analysis was performed using R 4.2.2 Statistical significance was set at $P < 0.05$ (two-sided) for all tests.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence from the meta-analysis for each outcome and dose type. In this approach, we used five domains, namely the risk of bias, inconsistency, indirectness, imprecision and publication bias to quantify the certainty of evience into very low, moderate or high certainty of evidence.[13]

Human participants protection

Ethics committee approval was not obtained as this was only a review of previously published studies.

Results

We identified 328 articles in PubMed and 79 in Embase. After removing duplicates, we screened the titles and abstracts of 380

articles for eligibility. Furthermore, we screened the full text of 36 articles and found 18 that met the eligibility criteria. We identified two additional articles by searching Google Scholar, the WHO-COVID-19 research database, medRxiv, and the reference list of included articles. A total of 20 articles were included in the final analysis [Figure 1].[14-33]

All the studies were published during 2021–2022. Of the 20 studies included, 11 were from the United Kingdom, six from other European countries, one each from Argentina and Malaysia, and one with data from Europe and the United States of America [Supplemental Figure 1]. Studies were either self-controlled case series (n = 11) or cohort (n = 9) design. Seventeen studies included individuals aged more than 16 years, and the remaining three had adults and children.

Fourteen studies included individuals after the first dose, five after the first or second dose, and the remaining one after the second dose [Table 1].

All studies except one conducted the analysis using linked electronic health record databases. We observed wide variations in the types of outcomes included across the studies. Thrombocytopenia was included in 14 studies, any venous thromboembolic event in 13, myocardial infarction in 11, stroke and cerebral venous thrombosis in nine, arterial thromboembolic event in eight, and PVT in seven.

Three studies that met the eligibility criteria were not included in the quantitative synthesis because of the different measures of association reported. Pottegård A *et al.*[26] did a population-based cohort study to compare the adverse events observed within 28 days of vaccination with the expected rates from the general population during the pre-pandemic period and calculated the SMR. The SMR was 1.9 (95% CI: 1.5–2.5) for venous thromboembolic events and 20.3 (95% CI: 8.1–41.7) for cerebral venous thrombosis. Sturkenboom M *et al.*[30] conducted a cohort study using data from four European countries to monitor 29 adverse events of special interest after COVID-19 vaccination. The pooled random effects IRR for TTS was 2.98 (95% CI: 1.7–5.3). Higgins H *et al.*[19] assessed the risk of clinically ascertained TTS cases after the first dose of the ChAdOx1-S vaccine by using a self-controlled case series design. The relative incidence of TTS was 5.67 in the age group of 18–39 years during 4–27 days after vaccination compared to the baseline period.

Primary outcomes

Summary estimates indicated a significant increase in risk for central venous thrombosis (CVT) (IRR: 3.5; 95% CI: 2.2–5.4), PVT (IRR: 2; 95% CI: 1.1–3.5) and thrombocytopenia (IRR: 1.6; 95% CI: 1.4–1.9) after vaccination with the first dose of ChAdOx1-S vaccine compared to either pre-vaccinated or unvaccinated individuals or recipients of mRNA vaccines. However, no significant increase in the risk of those events was observed after the second dose [Figure 2]. GRADE approach showed high-to-moderate levels of certainty for the evidence against the first dose of vaccine for all primary outcomes [Table 2].
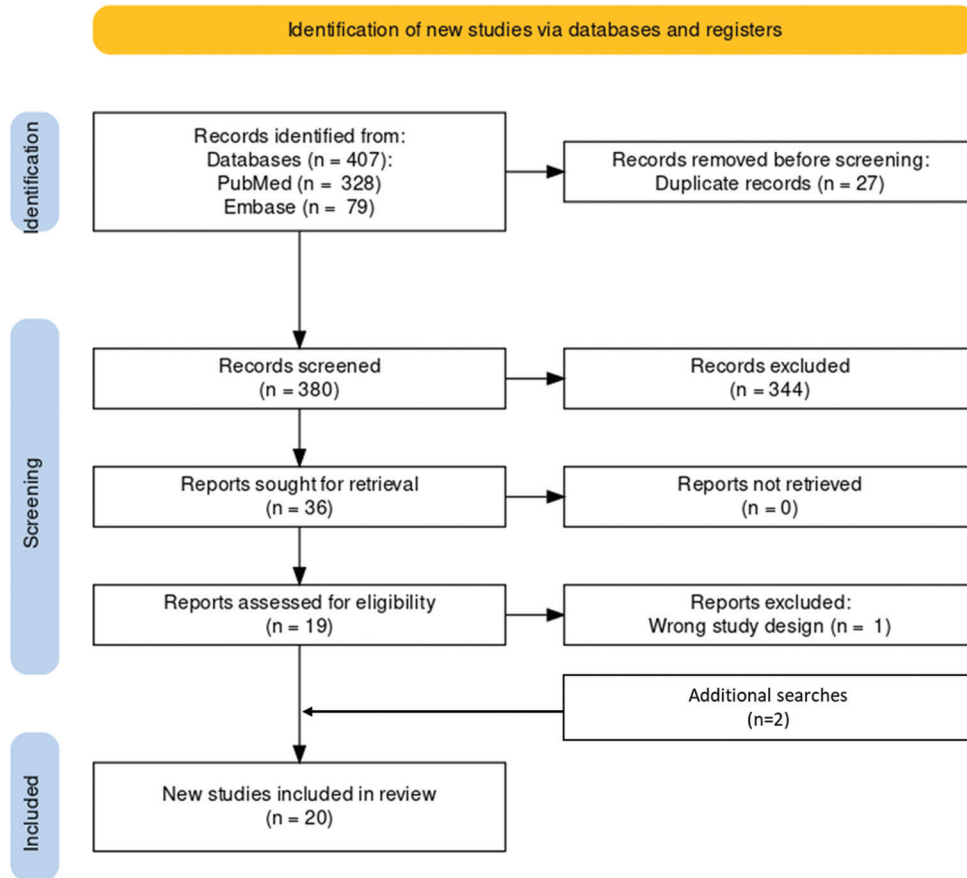
Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing identification, screening, and inclusion of studies

Secondary outcomes

Pooled estimates indicated no significant increase in risk for any of the secondary outcomes of interest: any thromboembolic event (arterial or venous), any hemorrhage, myocardial infarction or coronary artery disease and stroke (hemorrhagic or ischemic or others) post ChAdOx1-S vaccination after the first or second dose [Table 3, Supplemental Figure 2]. The GRADE levels of certainty of the evidence for most secondary outcomes were found to be very low or low [Supplemental Table 1].

Risk of bias, publication bias, and small study effects

Risk of bias assessment using Newcastle-Ottawa and Modified Newcastle-Ottawa tools found most of the studies (18 of 20) to be of good quality [Supplemental Table 2]. No evidence of significant publication bias could be found by visually examining the funnel plots [Supplemental Figure 3]. Funnel plots for the secondary outcomes showed possible evidence of publication bias for MI/CAD [Supplemental Figure 4].

DISCUSSION

Although several systematic reviews synthesized information from case reports and case series on demographics, clinical profile, and mortality due to vascular events following vaccination with ChAdOx1-S, ours is the first study that systematically reviewed all analytical studies testing the association between ChAdOx1-S vaccination and vascular events. We found that the first dose of the ChAdOx1-S vaccine was positively associated with CVT, PVT, and thrombocytopenia. The certainty of evidence using the GRADE approach was moderate to high. Our finding supports the recommendation to list cerebral venous sinus thrombosis and thrombocytopenia as very rare adverse events of ChAdOx1-S in the product information brochure,[7] and the recommendation to include thrombosis with TTS was listed as a very rare adverse event following the ChAdOx1-S vaccination.[3]

Most of the studies included in this review were done in European countries. A study on the geographical distribution of TTS cases using the AstraZeneca global safety database (till August 31, 2021) found the rates (cases per million doses administered per 21 days) ranging between 17.6 in Nordic countries and 0.2 in Asia and Brazil. The difference in rates could be due to variations in reporting.[34] Countries like India used SII COVISHIELD™ (same formulation as ChAdOx1-S) to administer approximately 1.7 billion doses. However, few case reports on VITT were publicly available. A lack of proper reporting mechanisms from India led to gaps in diagnosis, surveillance, and reporting.[35]
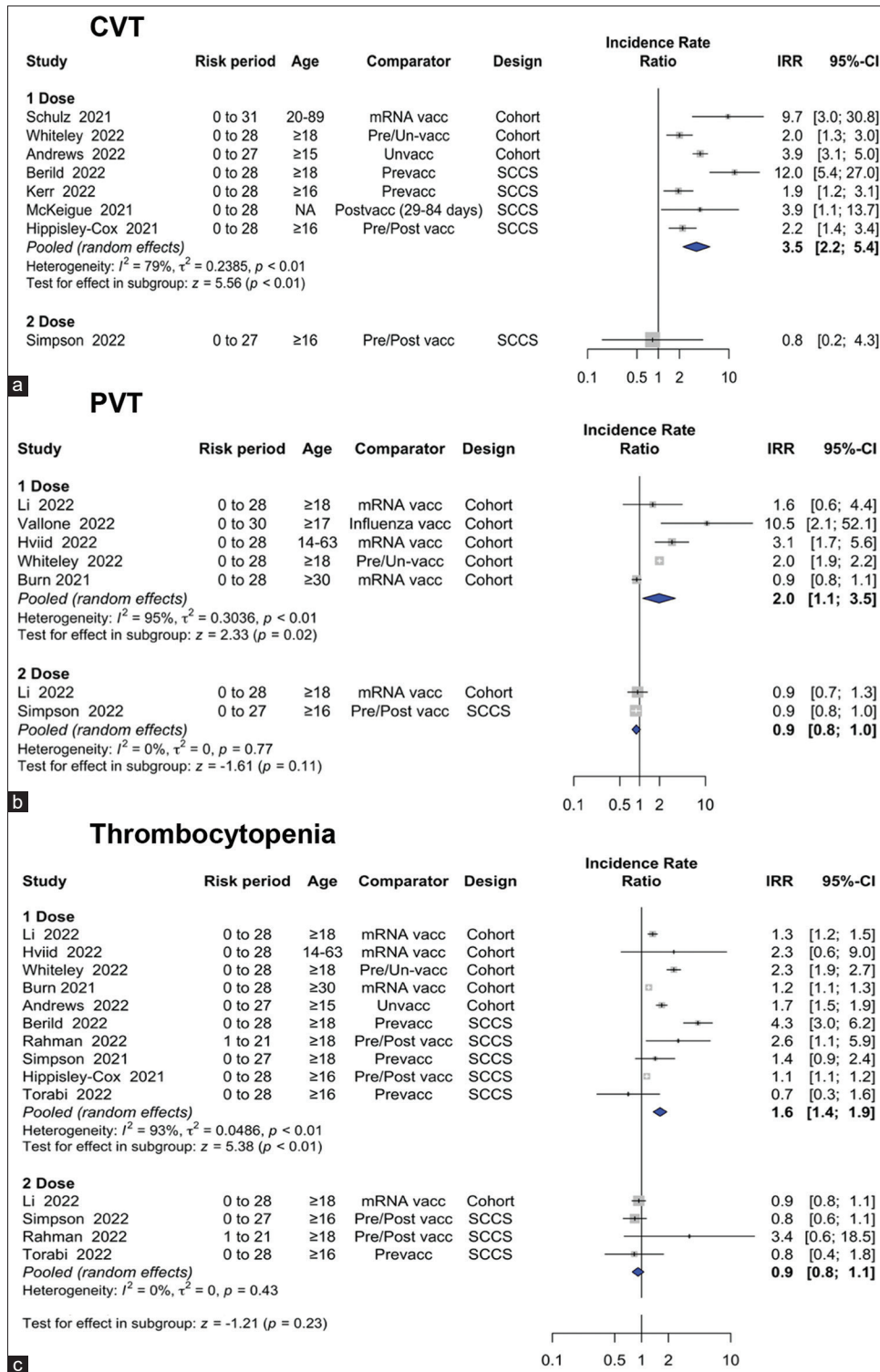
Figure 2: Forest plot for the pooled estimates of primary outcomes of interest among persons vaccinated with ChAdOx1 vaccines a) Central venous thrombosis b) Peripheral venous thrombosis c) Thrombocytopenia

Apart from vaccination, infection with SAR-CoV-2 was also identified as a risk factor for thromboembolic events. Katsoularis I *et al.*[36] did a self-controlled case series study and estimated the IRR of 5.9 for deep vein thrombosis, 31.6 for pulmonary embolism, and 2.5 for bleeding during 1–30 days after COVID-19. Knight R *et al.*[37] did a population-based cohort study and found that the hazard ratio for first arterial thrombosis after COVID-19 compared to no COVID-19 declined from 21.7 in the first week after COVID-19 to 1.34 in weeks 27–49. Similarly, the hazard ratio for the first venous thromboembolic event declined from 33.2 in week 1 after COVID-19 to 1.8 in weeks 27–49.

Table 1: Characteristics of the studies included in the review

First author	Study design	Sample size	Age group	Doses studied	Comparator
Schulz JB	Cohort	62	20–89	1	mRNA vaccine
Pottegard A	Cohort	281,264	18–65	1	Background incidence
Burn E	Cohort	6,119,754	≥30	1	mRNA vaccine
Xintong Li	Cohort	32,800,000	≥18	1, 2	mRNA vaccine
Whiteley WN	Cohort	21,193,814	≥18	1	Pre/Unvaccinated
Andrews	Cohort	27,378,384	≥15	1	Unvaccinated
Hviid A	Cohort	355,209	14–63	1	mRNA vaccine
Vallone MG	Cohort	29,918	≥17	1	Influenza vaccine
Sturkenboom M	Cohort	12,117,458	0+	1, 2	Pre/Post-vaccination
McKeigue	Cohort	80,905	NA	1	Post-vaccination
Hippisley-Cox J	SCCS	29,121,633	≥16	1	Pre/Post-vaccination
Simpson CR	SCCS	2,530,000	≥18	1	Pre-vaccination
Patone M	SCCS	32,552,534	≥16	1	Pre-vaccination
Rahman NA	SCCS	20,202,054	≥18	1, 2	Pre/Post-vaccination
Higgins H	SCCS	170	≥18	1	Pre/Post-vaccination
Kerr S	SCCS	11,637,157	≥16	1	Pre-vaccination
Botton J	SCCS	46,500,000	18–74	1, 2	Pre/Post-vaccination
Torabi F	SCCS	2,062,144	≥16	1, 2	Pre-vaccination
Simpson CR	SCCS	3,600,000	≥16	2	Pre/Post-vaccination
Berild JD	SCCS	5,351,105	≥18	1	Pre-vaccination

SCCS: Self-controlled case series

Table 2: GRADE for certainty of evidence for the primary outcomes

Outcomes	IRR (95% CI)	No. of studies	Certainty of evidence (GRADE)	Comments
CVT after 1 dose	3.5 (2.2–5.4)	8 observational studies	High	First dose of ChAdOx1 results in a large increase in the risk of CVT.
CVT after 2 doses	0.8 (0.2–4.3)	1 observational study	Very low	The evidence is very uncertain about the effect of second dose of ChAdOx1 on CVT.
PVT after 1 dose	2.0 (1.1–3.5)	5 observational studies	High	First dose of ChAdOx1 results in a large increase in the risk of PVT.
PVT after 2 doses	0.9 (0.8–1)	2 observational studies	Moderate	Second dose of ChAdOx1 likely does not increase the risk of PVT.
Thrombocytopenia after 1 dose	1.6 (1.4–1.9)	10 observational studies	Moderate	First dose of ChAdOx1 likely results in a slight increase in the risk of thrombocytopenia.
Thrombocytopenia after 2 doses	0.9 (0.8–1.1)	4 observational studies	Low	Second dose of ChAdOx1 likely does not increase the risk of thrombocytopenia.

CVT: Cerebral venous thrombosis, PVT: Peripheral venous thrombosis

Table 3: Pooled incidence rate ratio (IRR) of secondary outcomes post ChAdOx1 vaccination

Outcome	Pooled IRR (95% CI)	
	1 Dose	**2 Dose**
Any venous thromboembolic event	1.3 (1.0, 1.7)	0.9 (0.8, 1.0)
Any arterial thromboembolic event	1.3 (0.9, 1.9)	1.0 (0.9, 1.0)
Any hemorrhage	1.0 (0.8, 1.3)	0.9 (0.8, 1.1)
Myocardial infarction/CAD	1.1 (0.8, 1.4)	1.0 (0.8, 1.2)
Stroke- Hemorrhagic	1.3 (0.9, 1.9)	1.1 (0.9, 1.4)
Stroke- Ischemic	1.1 (0.7, 1.6)	0.9 (0.9, 1.0)
Stroke- Others	1.2 (0.8, 1.8)	-

A few studies have compared the risk of thromboembolic events after ChAdOx1-S vaccination and SARS-CoV-2 infection. A self-controlled case series study conducted in England reported a higher IRR for venous thromboembolism 8–14 days after SARS-CoV-2 infection (13.86) than after ChAdOx1-S vaccination (1.10).[20] A cohort study estimated that the risk of cerebral venous sinus thrombosis after SARS-CoV-2 infection was 2.3 times higher than following ChAdOx1-S vaccination.[38] Risk-benefit analysis of ChAdOx1-S using a modeling approach found that the probability of dying from thrombosis after COVID-19 infection was 58–126 times higher than dying from TTS.[39] Therefore, the risk of thromboembolic events after ChAdOx1-S vaccination was lower than the risk after COVID-19 infection.

Limitations

Our review had several limitations. First, we did not include Ad26.COV2, an adenoviral vaccine, in our review. We restricted our analysis to the ChAdOx1-S vaccine as most of

the population had this vaccine, and only three of the studies included in our review evaluated the association between Ad26.COV2 vaccine and vascular events. Second, we used a RoB assessment tool proposed for self-controlled case series published in preprint.[11] The tool is not validated; thus, our RoB assessment may not be accurate in judging the quality of the included self-controlled case series. There is a need to validate the RoB assessment tool for self-controlled case series considering a recent increase in their application to assess vaccine safety.[40] Third, we did not account for variations in the comparison group chosen in different studies due to the lack of a sufficient number of studies in different subgroups. Finally, the lack of studies from low- and middle-income countries has implications for understanding the actual rates of thromboembolic events and establishing the cause-effect relationship in such populations.

Conclusions

This systematic review and meta-analysis found that the first dose of the ChAdOx1-S vaccine increased the risk of CVT, PVT, and thrombocytopenia by 2–3 times. For secondary outcomes such as any venous, arterial thromboembolic and hemorrhagic events, myocardial infarction, or coronary artery disease, we found no association or the certainty of the evidence was low to very low. As most studies were done in Europe, there is a need to establish databases at the national level in low- and middle-income countries to monitor rare adverse events in the post-marketing phase.

Conflicts of interest

There are no conflicts of interest.

References

1. Global COVID-19 Vaccination Strategy in a Changing World: July 2022 update. https://www.who.int/publications/m/item/global-covid-19-vaccination-strategy-in-a-changing-world--july-2022-update. [Last accessed on 2023 May 31].
2. WHO. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. 2022. https://covid19.who.int/. [Last accessed on 2023 May 31].
3. Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222 Vaxzevria™, SII COVISHIELD™). https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1. [Last accessed on 2023 May 31].
4. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384:2092-101.
5. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, *et al*. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124-30.
6. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. BMJ 2021;372:n699. doi: 10.1136/bmj.n699.
7. EMA. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low platelets. European Medicines Agency. Published April 6, 2021. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood. [Last accessed on 2023 May 31].
8. Mouta Nunes de Oliveira P, Mendes-de-Almeida DP, Bertollo Gomes Porto V, Crespo Cordeiro C, Vitiello Teixeira G, Saraiva Pedro R, *et al*. Vaccine-induced immune thrombotic thrombocytopenia after COVID-19 vaccination: Description of a series of 39 cases in Brazil. Vaccine 2022;40:4788-95.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
10. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210. doi: 10.1186/s13643-016-0384-4.
11. Wachira VK, Peixoto HM, Oliveira MRF de. Proposal of a quality assessment tool for the evaluation of the methodological quality of self-controlled case series and self-controlled risk interval study designs. SciELO Preprints 2022. doi: 10.1590/SciELOPreprints.4141.
12. Miettinen O. Estimability and estimation in case-referent studies. Am J Epidemiol 1976;103:226-35.
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
14. Ab Rahman N, Lim MT, Lee FY, Lee SC, Ramli A, Saharudin SN, *et al*. Risk of serious adverse events after the BNT162b2, CoronaVac, and ChAdOx1 vaccines in Malaysia: A self-controlled case series study. Vaccine 2022;40:4394-402.
15. Andrews NJ, Stowe J, Ramsay ME, Miller E. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: A national cohort study in England. Lancet Reg Health Eur 2022;13:100260. doi: 10.1016/j.lanepe.2021.100260.
16. Botton J, Jabagi MJ, Bertrand M, Baricault B, Drouin J, Le Vu S, *et al*. Risk for myocardial infarction, stroke, and pulmonary embolism following COVID-19 vaccines in adults younger than 75 years in France. Ann Intern Med 2022;175:1250-7.
17. Burn E, Li X, Delmestri A, Duarte-Salles T, Reyes C, Martinez-Hernandez E, *et al*. Thrombosis and thrombocytopenia after vaccination against and infection with SARS-CoV-2 in the United Kingdom. Nat Commun 2022;13:7167. doi: 10.1038/s41467-022-34668-w.
18. Dag Berild J, Bergstad Larsen V, Myrup Thiesson E, Lehtonen T, Grøsland M, Helgeland J, *et al*. Analysis of thromboembolic and thrombocytopenic events after the AZD1222, BNT162b2, and MRNA-1273 COVID-19 vaccines in 3 Nordic countries. JAMA Netw Open 2022;5:e2217375. doi: 10.1001/jamanetworkopen.2022.17375.
19. Higgins H, Andrews N, Stowe J, Amirthalingam G, Ramsay M, Bahra G, *et al*. Risk of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination prior to the recognition of vaccine-induced thrombocytopenia and thrombosis: A self-controlled case series study in England. Res Pract Thromb Haemost 2022;6:e12698. doi: 10.1002/rth2.12698.
20. Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, *et al*. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: Self-controlled case series study. BMJ 2021;374:n1931. doi: 10.1136/bmj.n1931.
21. Hviid A, Hansen JV, Thiesson EM, Wohlfahrt J. Association of AZD1222 and BNT162b2 COVID-19 vaccination with thromboembolic and thrombocytopenic events in frontline personnel: A retrospective cohort study. Ann Intern Med 2022;175:541-6.
22. Kerr S, Joy M, Torabi F, Bedston S, Akbari A, Agrawal U, *et al*. First dose ChAdOx1 and BNT162b2 COVID-19 vaccinations and cerebral venous sinus thrombosis: A pooled self-controlled case series study of 11.6 million individuals in England, Scotland, and Wales. PLoS Med 2022;19:e1003927. doi: 10.1371/journal.pmed.1003927.
23. Li X, Burn E, Duarte-Salles T, Yin C, Reich C, Delmestri A, *et al*. Comparative risk of thrombosis with thrombocytopenia syndrome or

thromboembolic events associated with different covid-19 vaccines: International network cohort study from five European countries and the US. BMJ 2022;379:e071594. doi: 10.1136/bmj-2022-071594.

24. McKeigue PM, Burgul R, Bishop J, Robertson C, McMenamin J, O'Leary M, *et al*. Association of cerebral venous thrombosis with recent COVID-19 vaccination: Case-crossover study using ascertainment through neuroimaging in Scotland. BMC Infect Dis 2021;21:1275. doi: 10.1186/s12879-021-06960-5.

25. Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S, *et al*. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med 2021;27:2144-53.

26. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, *et al*. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: Population based cohort study. BMJ 2021;373:n1114. doi: 10.1136/bmj.n1114.

27. Schulz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, *et al*. COVID-19 vaccine-associated cerebral venous thrombosis in Germany. Ann Neurol 2021;90:627-39.

28. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, *et al*. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Med 2021;27:1290-7.

29. Simpson CR, Kerr S, Katikireddi SV, McCowan C, Ritchie LD, Pan J, *et al*. Second-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Commun 2022;13:4800. doi: 10.1038/s41467-022-32264-6.

30. Sturkenboom M, Messina D, Paoletti O, de Burgos-Gonzalez A, García-Poza P, Huerta C, *et al*. Cohort monitoring of 29 adverse events of special interest prior to and after COVID-19 vaccination in four large European electronic healthcare data sources. MedRxiv 2022. doi: 10.1101/2022.08.17.22278894.

31. Torabi F, Bedston S, Lowthian E, Akbari A, Owen RK, Bradley DT, *et al*. Risk of thrombocytopenic, haemorrhagic and thromboembolic disorders following COVID-19 vaccination and positive test: A self-controlled case series analysis in Wales. Sci Rep 2022;12:16406. doi: 10.1038/s41598-022-20118-6.

32. Vallone MG, Falcón AL, Castro HM, Ferraris A, Cantarella RF, Staneloni MI, *et al*. Thrombotic events following Covid-19 vaccines compared to Influenza vaccines. Eur J Intern Med 2022;99:82-8.

33. Whiteley WN, Ip S, Cooper JA, Bolton T, Keene S, Walker V, *et al*. Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, or thrombocytopenic events: A population-based cohort study of 46 million adults in England. PLoS Med 2022;19:e1003926. doi: 10.1371/journal.pmed.1003926.

34. Soboleva K, Shankar NK, Yadavalli M, Ferreira C, Foskett N, Putsepp K, *et al*. Geographical distribution of TTS cases following AZD1222 (ChAdOx1 nCoV-19) vaccination. Lancet Glob Health 2022;10:e33-4.

35. John CV, Kumar R, Sivan AK, Jithin S, Abraham R, Philip CC. Vaccine-induced thrombotic thrombocytopenia (VITT): First report from India. Thromb J 2022;20:11. doi: 10.1186/s12959-022-00370-6.

36. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Jerndal H, Lundevaller EH, Sund M, *et al*. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: Nationwide self-controlled cases series and matched cohort study. BMJ 2022;377:e069590. doi: 10.1136/bmj-2021-069590.

37. Knight R, Walker V, Ip S, Cooper JA, Bolton T, Keene S, *et al*. Association of COVID-19 with major arterial and venous thrombotic diseases: A population-wide cohort study of 48 million adults in England and Wales. Circulation 2022;146:892-906.

38. Ohaeri C, Thomas DR, Salmon J, Cottrell S, Lyons J, Akbari A, *et al*. Comparative risk of cerebral venous sinus thrombosis (CVST) following COVID-19 vaccination or infection: A national cohort study using linked electronic health records. Hum Vaccines Immunother 2022;18:2127572. doi: 10.1080/21645515.2022.2127572.

39. Lau CL, Mayfield HJ, Sinclair JE, Brown SJ, Waller M, Enjeti AK, *et al*. Risk-benefit analysis of the AstraZeneca COVID-19 vaccine in Australia using a Bayesian network modelling framework. Vaccine 2021;39:7429-40.

40. Nie X, Xu L, Bai Y, Liu Z, Liu Z, Farrington P, *et al*. Self-controlled case series design in vaccine safety: A systematic review. Expert Rev Vaccines 2022;21:313-24.

Association between COVID-19 vaccination (ChAdOx1-S) and thromboembolic, thrombocytopenic, haemorrhagic events: A systematic review and meta-analysis of analytical epidemiological studies

Table of contents

Appendix 1: Systematic reviews of case reports/series of thromboembolic events following COVID-19 vaccination[1–10]

Author	Vaccine	Outcome	# studies	# cases	Key findings
Sharifian-Dorche M 2021	ChAdOx1, Ad26.COV2	Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis	14	49	• 36 cases after ChAdOx1, 13 cases after Ad26.COV2 vaccination • Majority females • Symptom onset within 1 week after 1st dose (range 4-19 days) • Headache was most common presenting symptom • Of the 49 cases, 24 had intracranial and subarachnoid haemorrhage • PF4 IgG Assay and d-Dimer was positive in most cases • Out of 49 cases, 19 died due to complications
Waqar U 2021	ChAdOx1, Ad26.COV2	Thrombosis with thrombocytopenia syndrome	62	160	• 67 8% (101/160) were females • Median age 42 5 years (IQR: 22) • TTS onset occurred in a median of 9 days after vaccination • 140 of 160 cases received ChAdOx1 vaccine • Venous thrombosis was most common (97/160[61 0%]) • Most cases had cerebral venous sinus thrombosis (106/160[66 3%]) • Female and individuals <45 years were more likely to have cerebral venous sinus thrombosis compared to male and ≥45 years • 47 (36 2%) died
Matar RH 2021	ChAdOx1	Outcomes of thromboembolic events	45	144	• 64 6% women • Mean age 21-68 years • Head ache, intracerebral haemorrhage, hemiparesis were common presenting adverse events • Cerebral venous sinus thrombosis (38 5%) followed by deep vein thrombosis/pulmonary embolism (21 1%) were common thromboembolic events • 39 patients died
Jaiswal V 2022	ChAdOx1, Ad26. COV2, mRNA	Cerebral Venous Sinus Thrombosis	25	80	• 59 (73 8%) were male • Mean age 42 9±13 9 years • 70 received adenoviral vector and the rest had mRNA vaccine • Mean time for onset of symptoms after vaccination was 11 1±5 3 days • Intracerebral haemorrhage occurred in 35 cases • Anti-PF-4 was positive in 45 cases • 31 died (39 2%)
Elberry MH 2022	ChAdOx1, Ad26.COV2	Thrombosis and thrombocytopenia	26	173	• 157 had ChAdOx1 and 16 had Ad26.COV2 • 74 6% were female and mean age was 43 2 (±16 7) • Average time from vaccination to admission was 10 5 to 15 9 days • Common thromboembolic events reported were cerebral venous sinus thrombosis, deep vein thrombosis, and pulmonary embolism • 52 were positive for antibodies against PF4 • 28 (16 2%) died
Kim AY 2022	ChAdOx1, Ad26.COV2	Vaccine induced immune thrombotic thrombocytopenia	18	664	• Mean age was 45 6 years • 70% were females • 54% had cerebral venous thrombosis • 91% was positive for anti-PF4 antibody test • 32% died • Incidence of total venous thrombosis was 28 (95% CI: 12-52) per 100,000 doses administered
Saluja P 2022	ChAdOx1, Ad26.COV2 mRNA vaccine	Thrombotic thrombocytopenic purpura	23	27	• Mean age was 51 3 years • 51 1% were female • TTP episodes were mostly after BNT162b2 vaccine followed by mRNA-1273 vaccine • One died

Appendix 1: Contd...

Author	Vaccine	Outcome	# studies	# cases	Key findings
Saluja P 2022	ChAdOx1, Ad26.COV2 mRNA vaccine	Post-vaccine immune thrombocytopenia	43	66	• Median age 52 years (range: 19-86 years) • 60 6% were females • Mean time from vaccine administration and symptom onset was 8 4 days • 73% cases were after first dose • More ITP events after mRNA vaccines compared to adenoviral • No deaths
Bidari A 2022	ChAdOx1, Ad26.COV2 mRNA vaccine	Immune thrombocytopenic purpura after COVID-19 vaccination	41	77	• Median age was 54 years (IQR: 36-72 years) • 75 4% cases were reported after mRNA vaccines • 79 2% cases were after first dose of vaccination • 75% developed ITP within 12 days of vaccination • One case died due to intracranial haemorrhage
Song TJ 2023	ChAdOx1	Thrombosis with thrombocytopenia syndrome (TTS)	19	64	• 38 (59 3%) had cerebral venous thrombosis • Median age of patients with CVT was 36 5 years and 73 3% were female • Patients with CVT were younger and had lower fibrinogen levels than those without CVT

REFERENCES

1. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607. https://doi.org/10.1016/j.jns.2021.117607.

2. Waqar U, Ahmed S, Gardezi SMHA, Tahir MS, Abidin ZU, Hussain A, et al. Thrombosis with Thrombocytopenia Syndrome After Administration of AZD1222 or Ad26.COV2.S Vaccine for COVID-19: A Systematic Review. Clin Appl Thromb Hemost 2021;27:10760296211068488. https://doi.org/10.1177/10760296211068487.

3. Matar RH, Than CA, Nakanishi H, Daniel RS, Smayra K, Sim BL, et al. Outcomes of patients with thromboembolic events following coronavirus disease 2019 AstraZeneca vaccination: A systematic review and meta-analysis. Blood Coagul Fibrinolysis 2022;33:90–112. https://doi.org/10.1097/MBC.0000000000001113.

4. Jaiswal V, Nepal G, Dijamco P, Ishak A, Dagar M, Sarfraz Z, et al. Cerebral Venous Sinus Thrombosis Following COVID-19 Vaccination: A Systematic Review. J Prim Care Community Health 2022;13:21501319221074450. https://doi.org/10.1177/21501319221074450.

5. Elberry MH, Abdelgawad HAH, Hamdallah A, Abdella WS, Ahmed AS, Ghaith HS, et al. A systematic review of vaccine-induced thrombotic thrombocytopenia in individuals who received COVID-19 adenoviral-vector-based vaccines. J Thromb Thrombolysis 2022;53:798–823. https://doi.org/10.1007/s11239-021-02626-w.

6. Kim AY, Woo W, Yon DK, Lee SW, Yang JW, Kim JH, et al. Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A Systematic Review and Meta-Analysis. Int J Infect Dis 2022;119:130–9. https://doi.org/10.1016/j.ijid.2022.03.034.

7. Saluja P, Amisha F, Gautam N, Goraya H. A Systematic Review of Reported Cases of Immune Thrombocytopenia after COVID-19 Vaccination. Vaccines (Basel) 2022;10:1444. https://doi.org/10.3390/vaccines10091444.

8. Saluja P, Gautam N, Yadala S, Venkata AN. Thrombotic thrombocytopenic purpura (TTP) after COVID-19 vaccination: A systematic review of reported cases. Thromb Res 2022;214:115–21. https://doi.org/10.1016/j.thromres.2022.04.020.

9. Bidari A, Asgarian S, Pour Mohammad A, Naderi D, Anaraki SR, Gholizadeh Mesgarha M, et al. Immune thrombocytopenic purpura secondary to COVID-19 vaccination: A systematic review. Eur J Haematol 2023;110:335–53. https://doi.org/10.1111/ejh.13917.

10. Song T-J, Shin JI, Yon DK, Lee SW, Hwang SY, Hwang J, et al. Cerebral venous thrombosis after ChAdOx1 nCoV-19 vaccination: A systematic review. Eur Rev Med Pharmacol Sci 2023;27:404–10. https://doi.org/10.26355/eurrev_202301_30894.

11. Wachira VK, Peixoto HM, Oliveira MRF de. Proposal of a Quality Assessment tool for the Evaluation of the Methodological Quality of Self-Controlled Case Series and Self-Controlled Risk Interval Study Designs 2022. https://doi.org/10.1590/SciELOPreprints.4141.

Inclusion criteria

Population	Populations eligible for Covid-19 vaccine
Intervention	ChadOx1 Covid-19 vaccine
Control groups	Unvaccinated/pre-vaccination/post-vaccination/other vaccines
Outcomes	Thromboembolic/thrombocytopenic/Haemorrhagic events
Study designs	Case control/two-group cohort/single group cohort with background incidence/self-controlled case series (SCCS)*/clinical trials
Time period	No restrictions
Language	No restrictions

Note: *Self-controlled case series (SCCS): The self-controlled case series (SCCS) method is an epidemiological study design originally developed for evaluation of vaccine safety for which individuals act as their own control and all time invariant confounding is eliminated.[1]

1. Petersen I, Douglas I, Whitaker H. Self-controlled case series methods: An alternative to standard epidemiological study designs. BMJ [Internet]. 2016 Sep 12 [cited 2023 Mar 27];354:i4515. Available from: https://www.bmj.com/content/354/bmj.i4515.

Exclusion criteria

Population	Studies exclusively on children or special populations
Intervention	Other covid vaccines
Outcomes	Non-thromboembolic or non-haemorrhagic outcomes
Study designs	Single group cohort with no comparison group

APPENDIX 3: SEARCH STRATEGY DETAILS

Embase: Carried out on 17/10/2022

1. 'vaxzevria'/exp
2. 'covid-19 vaccine astrazeneca' OR 'covid-19 vaccine astrazeneca-oxford' OR 'covid-19 vaccine oxford-astrazeneca' OR 'astrazeneca covid-19 vaccine' OR 'astrazeneca-oxford covid-19 vaccine' OR 'azd 1222' OR 'azd1222' OR 'chadox 1' OR 'chadox1 ncov 19' OR 'chadox1 covid-19 vaccine' OR 'chadox1 ncov 19' OR 'chadox1 ncov 19 vaccine' OR 'chadox1 ncov-19' OR 'chadox1 ncov19' OR 'chadox1 s' OR 'chadox1-s' OR 'covishield' OR 'oxford-astrazeneca covid-19 vaccine' OR 'vaxzevria' OR covishield:ti,ab
3. 1 OR 2
4. 'thromboembolism'/exp
5. 'cerebral embolism and thrombosis' OR 'embolism and thrombosis' OR 'embolism, thrombo'
6. 'intracranial embolism and thrombosis' OR 'thrombo embolic disease' OR 'thrombo embolism' OR 'thrombo-emboli' OR 'thrombo-embolus' OR 'thromboemboli' OR 'thromboembolic' OR 'thromboembolic complication' OR 'thromboembolic disease' OR 'thromboembolic process' OR 'thromboembolism' OR 'thromboembolus' OR 'thromboemboly'
7. 'cerebrovascular accident'/exp
8. 'cva' OR 'accident, cerebrovascular' OR 'acute cerebrovascular lesion' OR 'acute focal cerebral vasculopathy' OR 'acute stroke' OR 'apoplectic stroke' OR 'apoplexia' OR 'apoplexy' OR 'blood flow disturbance, brain' OR 'brain accident' OR 'brain attack' OR 'brain blood flow disturbance' OR 'brain insult' OR 'brain insultus' OR 'brain vascular accident' OR 'cerebral apoplexia' OR 'cerebral insult' OR 'cerebral stroke' OR 'cerebral vascular accident' OR 'cerebral vascular insufficiency' OR 'cerebro vascular accident' OR 'cerebrovascular accident' OR 'cerebrovascular arrest' OR 'cerebrovascular failure' OR 'cerebrovascular injury' OR 'cerebrovascular insufficiency' OR 'cerebrovascular insult' OR 'cerebrum vascular accident' OR 'cryptogenic stroke' OR 'insultus cerebralis' OR 'ischaemic seizure' OR 'ischemic seizure' OR 'stroke' OR 'thrombotic stroke'
9. 4 OR 5 OR 6 OR 7 OR 8
10. 'heart infarction'/exp
11. 'cardiac infarct' OR 'cardiac infarction' OR 'cardial infarct' OR 'heart attack' OR 'heart infarct' OR 'heart infarction' OR 'heart micro infarction' OR 'heart muscle infarction' OR 'infarction, heart' OR 'myocardial infarct' OR 'myocardial infarction' OR 'myocardium infarct' OR 'myocardium infarction' OR 'premonitory infarction sign' OR 'second heart

attack' OR 'subendocardial infarction' OR 'transmural cardiac infarction' OR 'transmural heart infarction' OR 'transmural infarction, heart'

12. 'acute coronary syndrome'/exp
13. 'acute coronary syndrome' OR 'acute coronary syndromes'
14. 10 OR 11 OR 12 OR 13
15. 'deep vein thrombosis'/exp
16. 'dvt (deep vein thrombosis)' OR 'acute dvt' OR 'acute deep venous thrombosis' OR 'deep thrombo-phlebitis' OR 'deep thrombophlebitis' OR 'deep vein blood clots' OR 'deep vein thrombophlebitis' OR 'deep vein thrombosis' OR 'deep vein thrombus' OR 'deep venous thrombophlebitis' OR 'deep venous thrombosis' OR 'deep venous thrombus' OR 'recurrent dvt' OR 'thrombosis, acute deep venous'
17. 15 OR 16
18. 'lung embolism'/exp
19. 'chronic lung embolism' OR 'embolism, lung' OR 'lung embolism' OR 'lung embolization' OR 'lung embolus' OR 'lung embolus recurrence' OR 'lung emboly' OR 'lung microembolism' OR 'lung microembolization' OR 'lung microembolus' OR 'lung thromboembolism' OR 'microembolus, lung' OR 'pulmonary embolism' OR 'pulmonary embolization' OR 'pulmonary embolus' OR 'pulmonary microembolism' OR 'pulmonary thromboembolic disease' OR 'pulmonary thromboembolism' OR 'thromboembolism, lung'
20. 18 OR 19
21. 'thrombocyte disorder'/exp OR 'blood platelet disorders' OR 'congenital thrombocytopathy' OR 'platelet storage pool deficiency' OR 'thrombocyte disease' OR 'thrombocyte disorder' OR 'thrombocytopathia' OR 'thrombocytopathy'
22. 9 OR 14 OR 17 OR 20 OR 21
23. 'case control study'/exp
24. 'case control study' OR 'case-control studies' OR 'case-control study' OR 'control study, case' OR 'matched case control' OR 'matched case control studies' OR 'matched case control study'
25. 23 OR 24
26. 'cohort analysis'/exp
27. 'analysis, cohort' OR 'cohort analysis' OR 'cohort fertility' OR 'cohort life cycle' OR 'cohort studies' OR 'cohort study'
28. 26 OR 27
29. 'self controlled case series'/exp
30. 'controlled clinical trial'/exp
31. 'clinical trial, controlled' OR 'controlled clinical comparison' OR 'controlled clinical drug trial' OR 'controlled clinical experiment' OR 'controlled clinical study' OR 'controlled clinical test' OR 'controlled clinical trial'
32. 30 OR 31
33. 'analytical study'/exp
34. 25 OR 28 OR 29 OR 32 OR 33
35. 3 AND 22 AND 34.

PubMed: Carried out on 18/10/2022

1. 'vaxzevria'
2. 'covid-19 vaccine astrazeneca' OR 'covid-19 vaccine astrazeneca-oxford' OR 'covid-19 vaccine oxford-astrazeneca' OR 'astrazeneca covid-19 vaccine' OR 'astrazeneca-oxford covid-19 vaccine' OR 'azd 1222' OR 'azd1222' OR 'chadox1' OR 'chadox1 ncov 19' OR 'chadox1 covid-19 vaccine' OR 'chadox1 ncov 19' OR 'chadox1 ncov 19 vaccine' OR 'chadox1 ncov-19' OR 'chadox1 ncov19' OR 'chadox1 s' OR 'chadox1-s' OR 'covishield' OR 'oxford-astrazeneca covid-19 vaccine' OR 'vaxzevria' OR covishield:ti,ab
3. 1 OR 2
4. 'thromboembolism'
5. 'cerebral embolism and thrombosis' OR 'embolism and thrombosis' OR 'embolism, thrombo'
6. 'intracranial embolism and thrombosis' OR 'thrombo embolic disease' OR 'thrombo embolism' OR 'thrombo-emboli' OR 'thrombo-embolus' OR 'thromboemboli' OR 'thromboembolic' OR 'thromboembolic complication' OR 'thromboembolic disease' OR 'thromboembolic process' OR 'thromboembolism' OR 'thromboembolus' OR 'thromboemboly'
7. 'cerebrovascular accident'
8. 'cva' OR 'accident, cerebrovascular' OR 'acute cerebrovascular lesion' OR 'acute focal cerebral vasculopathy' OR 'acute stroke' OR 'apoplectic stroke' OR 'apoplexia' OR 'apoplexy' OR 'blood flow disturbance, brain' OR 'brain accident' OR 'brain attack' OR 'brain blood flow disturbance' OR 'brain insult' OR 'brain insultus' OR 'brain vascular accident' OR 'cerebral apoplexia' OR 'cerebral insult' OR 'cerebral stroke' OR 'cerebral vascular accident' OR 'cerebral vascular insufficiency' OR 'cerebro vascular accident' OR 'cerebrovascular accident' OR 'cerebrovascular arrest' OR 'cerebrovascular failure' OR 'cerebrovascular

injury' OR 'cerebrovascular insufficiency' OR 'cerebrovascular insult' OR 'cerebrum vascular accident' OR 'cryptogenic stroke' OR 'insultus cerebralis' OR 'ischaemic seizure' OR 'ischemic seizure' OR 'stroke' OR 'thrombotic stroke'

9. 4 OR 5 OR 6 OR 7 OR 8
10. 'heart infarction'
11. 'cardiac infarct' OR 'cardiac infarction' OR 'cardial infarct' OR 'heart attack' OR 'heart infarct' OR 'heart infarction' OR 'heart micro infarction' OR 'heart muscle infarction' OR 'infarction, heart' OR 'myocardial infarct' OR 'myocardial infarction' OR 'myocardium infarct' OR 'myocardium infarction' OR 'premonitory infarction sign' OR 'second heart attack' OR 'subendocardial infarction' OR 'transmural cardiac infarction' OR 'transmural heart infarction' OR 'transmural infarction, heart'
12. 'acute coronary syndrome'
13. 'acute coronary syndrome' OR 'acute coronary syndromes'
14. 10 OR 11 OR 12 OR 13
15. 'deep vein thrombosis'
16. 'dvt (deep vein thrombosis)' OR 'acute dvt' OR 'acute deep venous thrombosis' OR 'deep thrombo-phlebitis' OR 'deep thrombophlebitis' OR 'deep vein blood clots' OR 'deep vein thrombophlebitis' OR 'deep vein thrombosis' OR 'deep vein thrombus' OR 'deep venous thrombophlebitis' OR 'deep venous thrombosis' OR 'deep venous thrombus' OR 'recurrent dvt' OR 'thrombosis, acute deep venous'
17. 15 OR 16
18. 'lung embolism'
19. 'chronic lung embolism' OR 'embolism, lung' OR 'lung embolism' OR 'lung embolization' OR 'lung embolus' OR 'lung embolus recurrence' OR 'lung emboly' OR 'lung microembolism' OR 'lung microembolization' OR 'lung microembolus' OR 'lung thromboembolism' OR 'microembolus, lung' OR 'pulmonary embolism' OR 'pulmonary embolization' OR 'pulmonary embolus' OR 'pulmonary microembolism' OR 'pulmonary thromboembolic disease' OR 'pulmonary thromboembolism' OR 'thromboembolism, lung'
20. 18 OR 19
21. 'thrombocyte disorder'OR 'blood platelet disorders' OR 'congenital thrombocytopathy' OR 'platelet storage pool deficiency' OR 'thrombocyte disease' OR 'thrombocyte disorder' OR 'thrombocytopathia' OR 'thrombocytopathy'
22. 9 OR 14 OR 17 OR 20 OR 21
23. 'case control study'
24. 'case control study' OR 'case-control studies' OR 'case-control study' OR 'control study, case' OR 'matched case control' OR 'matched case control studies' OR 'matched case control study'
25. 23 OR 24
26. 'cohort analysis'
27. 'analysis, cohort' OR 'cohort analysis' OR 'cohort fertility' OR 'cohort life cycle' OR 'cohort studies' OR 'cohort study'
28. 26 OR 27
29. 'self controlled case series'
30. 'controlled clinical trial'
31. 'clinical trial, controlled' OR 'controlled clinical comparison' OR 'controlled clinical drug trial' OR 'controlled clinical experiment' OR 'controlled clinical study' OR 'controlled clinical test' OR 'controlled clinical trial'
32. 30 OR 31
33. 'analytical study'
34. 25 OR 28 OR 29 OR 32 OR 33
35. 3 AND 22 AND 34.

WHO Covid-19 database: Carried out on 26/11/2022

(chadox OR azd 1222 OR "Oxford-Astrazeneca") AND (thromboembolism OR "Central venous thrombosis" OR thrombocytopenia OR stroke OR "Myocardial infarction" OR hemorrhage) AND type_of_study:("observational_studies" OR "cohort_studies").

Google Scholar: Carried out on 26/11/20221

(chadox OR azd 1222 OR "Oxford-Astrazeneca") AND (thromboembolism OR "Central venous thrombosis" OR thrombocytopenia OR stroke OR "Myocardial infarction" OR hemorrhage) AND type_of_study:("observational_studies" OR "cohort_studies").

medRxiv: Carried out on 27/11/2022

1. Chadox OR AZD 1222 OR Oxford-Aztrazeneca
2. Chadox AND Thrombocytopenia
3. Chadox AND Thromboembolism
4. Chadox AND Adverse events

5. Chadox AND Myocardial infarction
6. Chadox AND Hemorrhage
7. Chadox AND Stroke.

Appendix 4: Risk and comparison period in self-controlled case series		
Study	Risk period	Comparison
Berild JD	28 days following vaccination	Pre-vaccination period (2020-21) covering four seasons (March-May, June-August, September-November, Dec-Feb)
Botton J	3 weeks after vaccination with first/second dose	All other period of observation from 6 Feb 2021 to 20 July 2021
Rahman N	21 days post vaccination	All other period between 1 Feb and 30 Sept 2021
Higgins	27 days post vaccination	All other period between Jan 1 to March 31
Kerr S	28 days post vaccination	90 days before vaccination
Hippisley-Cox	28 days post vaccination	All other period between 1 Dec 2020 and 24 April 2021
Simpson CR	28 days post vaccination	15 to 104 days before receipt of vaccination
Torabi F	28 days post vaccination	15 to 104 days before receipt of vaccination
Patone M	28 days post vaccination	All other period between 1 Dec 2020 to 31 May 2021

APPENDIX 5: DESCRIPTION OF THE RISK OF BIAS ASSESSMENT TOOLS USED

Ottawa-Newcastle tool for ROB assessment of cohort studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative *(one star)*
   b) Somewhat representative *(one star)*
   c) Selected group
   d) No description of the derivation of the cohort.

2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort *(one star)*
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort.

3) Ascertainment of exposure
   a) Secure record (e.g., surgical record) *(one star)*
   b) Structured interview *(one star)*
   c) Written self-report
   d) No description
   e) Other.

4) Demonstration that outcome of interest was not present at start of study
   a) Yes *(one star)*
   b) No.

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
   a) The study controls for age, sex, and marital status *(one star)*
   b) Study controls for other factors (list) _____ *(one star)*
   c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders.

Outcome

1) Assessment of outcome
   a) Independent blind assessment *(one star)*
   b) Record linkage *(one star)*
   c) Self report
   d) No description
   e) Other.

2) Was follow-up long enough for outcomes to occur
   a) Yes *(one star)*
   b) No.
   Indicate the median duration of follow-up and a brief rationale for the assessment above: _____

3) Adequacy of follow-up of cohorts
   a) Complete follow up- all subject accounted for *(one star)*
   b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. *(one star)*
   c) Follow up rate less than 80% and no description of those lost
   d) No statement.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: *3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.*

Fair quality: *2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain .*

Poor quality: *0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.*

APPENDIX 6: REFERENCES OF THE ARTICLES INCLUDED IN THE SYSTEMATIC REVIEW AND META-ANALYSIS[12–31]
Supplemental Table 2: Risk of bias in the included studies

REFERENCES

1. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607. https://doi.org/10.1016/j.jns.2021.117607.
2. Waqar U, Ahmed S, Gardezi SMHA, Tahir MS, Abidin ZU, Hussain A, *et al*. Thrombosis with Thrombocytopenia Syndrome After Administration of AZD1222 or Ad26.COV2.S Vaccine for COVID-19: A Systematic Review. Clin Appl Thromb Hemost 2021;27:10760296211068488. https://doi.org/10.1177/10760296211068487.
3. Matar RH, Than CA, Nakanishi H, Daniel RS, Smayra K, Sim BL, *et al*. Outcomes of patients with thromboembolic events following coronavirus disease 2019 AstraZeneca vaccination: A systematic review and meta-analysis. Blood Coagul Fibrinolysis 2022;33:90–112. https://doi.org/10.1097/MBC.0000000000001113.
4. Jaiswal V, Nepal G, Dijamco P, Ishak A, Dagar M, Sarfraz Z, *et al*. Cerebral Venous Sinus Thrombosis Following COVID-19 Vaccination: A Systematic Review. J Prim Care Community Health 2022;13:21501319221074450. https://doi.org/10.1177/21501319221074450.
5. Elberry MH, Abdelgawad HAH, Hamdallah A, Abdella WS, Ahmed AS, Ghaith HS, *et al*. A systematic review of vaccine-induced thrombotic thrombocytopenia in individuals who received COVID-19 adenoviral-vector-based vaccines. J Thromb Thrombolysis 2022;53:798–823. https://doi.org/10.1007/s11239-021-02626-w.
6. Kim AY, Woo W, Yon DK, Lee SW, Yang JW, Kim JH, *et al*. Thrombosis patterns and clinical outcome of COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A Systematic Review and Meta-Analysis. Int J Infect Dis 2022;119:130–9. https://doi.org/10.1016/j.ijid.2022.03.034.
7. Saluja P, Amisha F, Gautam N, Goraya H. A Systematic Review of Reported Cases of Immune Thrombocytopenia after COVID-19 Vaccination. Vaccines (Basel) 2022;10:1444. https://doi.org/10.3390/vaccines10091444.
8. Saluja P, Gautam N, Yadala S, Venkata AN. Thrombotic thrombocytopenic purpura (TTP) after COVID-19 vaccination: A systematic review of reported cases. Thromb Res 2022;214:115–21. https://doi.org/10.1016/j.thromres.2022.04.020.
9. Bidari A, Asgarian S, Pour Mohammad A, Naderi D, Anaraki SR, Gholizadeh Mesgarha M, *et al*. Immune thrombocytopenic purpura secondary to COVID-19 vaccination: A systematic review. Eur J Haematol 2023;110:335–53. https://doi.org/10.1111/ejh.13917.
10. Song T-J, Shin JI, Yon DK, Lee SW, Hwang SY, Hwang J, *et al*. Cerebral venous thrombosis after ChAdOx1 nCoV-19 vaccination: A systematic review. Eur Rev Med Pharmacol Sci 2023;27:404–10. https://doi.org/10.26355/eurrev_202301_30894.
11. Wachira VK, Peixoto HM, Oliveira MRF de. Proposal of a Quality Assessment tool for the Evaluation of the Methodological Quality of Self-Controlled Case Series and Self-Controlled Risk Interval Study Designs 2022. https://doi.org/10.1590/SciELOPreprints.4141.

Modified Ottawa-Newcastle tool for ROB assessment of Self-controlled cases series

Section	Explanation/Guide	Assessment
Selection		Three stars maximum
1) Representativeness of the cases	The study should show the representativeness of the cases in terms of all cases from the study population. For example, in vaccine safety studies, were the selected cases (people with the outcome of interest) representative of all cases originating from the study population?	One star maximum
a) Truly representative of the average _____ (describe) in the community * b) Somewhat representative of the average -_____ in the community * c) Selected group of users, example, volunteers d) No description of the derivation of the cases in the study	a) Were all eligible cases included in the study? In the case of vaccine safety studies, were all cases registered for example in a data base of adverse events, reference institution or hospital or was there a clear method of defining who was to be included in the study? b) In case of random sampling, was there a clear method used to define the cases included in the study? Example, In the case of vaccine safety studies were the adverse effects analyzed reported at a predetermined period of interest? c) Was there a certain group of individuals who qualified to be the cases after an exposure and were there any justifications of why that was done?	A study gets a star if meets the requirements for item a or b
d) No explanation whatsoever of how the cases were included in the follow up.		
2) Ascertainment of exposure a) Secure record (Example, data base) * b) Structured interview * c) Written self-report d) No description	The study should report how the exposure was ascertained a) Is there a secure record of that shows that there was an exposure? Example, in the case of vaccines, is there a secure database of the vaccines administered, doses, date, batch number? b) In the absence of a database or secure registries of the exposure of interest, were the cases interviewed to clarify about the exposure, did they show a vaccination card, were the caregivers contacted to confirm the information? c) Did the cases self-report the exposure with no other physical evidence (like a vaccination card)? Example, a self-report of vaccination d) No documented evidence of exposure or self-report.	One star maximum A study gets a star if it meets the requirements of item a or b.
3) Demonstration that outcome of interest was not present at start of study a) Yes* b) No	There should be evidence that the outcome of interest occurred during the observation period a) The study should report that the outcome of interest occurred during the observation period	One star maximum A study gets a star the response is "yes"
Comparability	One of the most important pillars of self-controlled studies. a) The study should at least report which of the confounding factors that vary over time were controlled for.	Two stars maximum
1) Comparability of cases on the basis of the design or analysis	The comparability is inherent of the study design and should be evaluated in detail	Two stars maximum
a) Study controls for _____ (select the most important factor that varies over time; seasonality or age) or the follow-up period was short enough to mitigate time-confounding issues * b) Study controls for any additional factor or justifies why the time varying factors were controlled (This criterion could be modified to indicate specific control for a second important factor that varies over time) *	a) e b) The study should report if a time varying factor such as seasonality or age were controlled in the study. (Some exposures depending on the age or seasonality may give biased results of the outcomes evaluated)	A study can get a star if it meets the requirements of item a or b, or two stars if it meets the requirements of the two.
Outcome	The study should clearly report the outcome of interest	Five stars maximum
1) Assessment of outcome	The outcome of interest should be evaluated in a valid manner	One star maximum
a) Independent blind assessment* or outcome was measured in a valid and reliable way b) Record linkage* c) Self-report d) No description	a) Were the outcomes evaluated in an independent way (by specialists who were blinded), was a valid and reliable method of evaluation used like a criterion of confirmation of exposure? b) In the case of the use of a database, were there any data linkage between the exposure database and that of outcomes? c) Did the cases self-report the outcomes? d) No description of how the outcome was assessed.	A study get a star if it meets the requirements of item a or b
2) Risk period stated	One of the observation periods of the SCCS and SCRI designs	One star maximum

Contd...

Section	Explanation/Guide	Assessment
a) Yes*/justify the period b) No	a) Was the risk period clearly stated in reference to when the exposure occurred, or the selection of the period justified? b) No statement of the risk period.	A study get a star if the response is "yes"
3) Control period stated	One of the observation periods of the SCCS and SCRI designs	Maximum of one star
a) Yes* b) No	a) Was the control period clearly stated in reference to the time of exposure or the risk period. b) No statement of the control period.	A study get a star if the response is "yes"
4) Risk period and control period long enough for outcomes to occur	The risk and control periods should be long enough to observe the outcomes of interest.	One star maximum
a) Yes (select an adequate follow up period for outcome of interest/)* b) No	a) Was there an adequate follow up? *An adequate follow up is essential to observe the desired outcomes. Generally, the period of risk is determined by previous studies. The study should at least mention why the lengths of the periods of observation were chosen, this information guides in determining if the follow up was sufficient enough for the outcomes to occur.	A study get a star if the response is "yes"
5) Adequacy of follow up of cases	Significant loss to follow up may be detrimental to the results obtained. A SCCS or SCRI should account for the cases studied.	One star maximum
a) Complete follow up - all subjects accounted for* b) Subjects lost to follow up unlikely to introduce bias - small number lost -> ____ % (select an adequate %) follow up, or description provided of those lost)* c) Follow up rate < ____% (select an adequate %) and no description of those lost d) No statement	a) Were all cases accounted for at the end of the study period? *All cases which should be accounted for. In case of a recurrent event or death, this should de clearly reported. b) If the cases are lost due to other motives like a personal choice to leave the study or lack of information (e.g., no exposure information) in a certain period of the follow up in case of databases, the possible impact should be reported and how it influences in the analysis. c) the follow up rate should be stated	A study gets a star if it meets the requirements for item a or b

Source: Wachira VK, Peixoto HM, Oliveira MRF de. Proposal of a Quality Assessment tool for the Evaluation of the Methodological Quality of Self-Controlled Case Series and Self-Controlled Risk Interval Study Designs [Internet]. 2022 May [cited 2023 Mar 27]. Available from: https://preprints.scielo.org/index.php/scielo/preprint/view/4141/version/4377
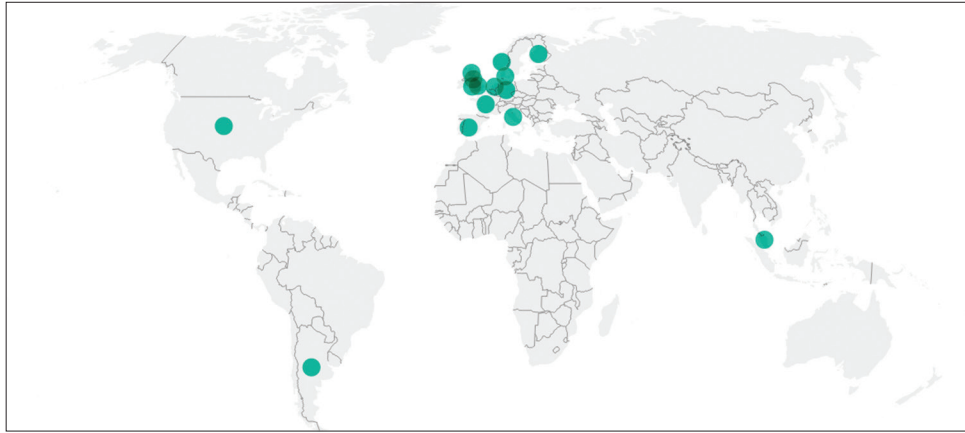
Supplemental Figure 1: Countries where the studies were conducted. Note: Green dots mark the country where the included studies were primarily carried out

Any VTE

Incidence Rate Ratio

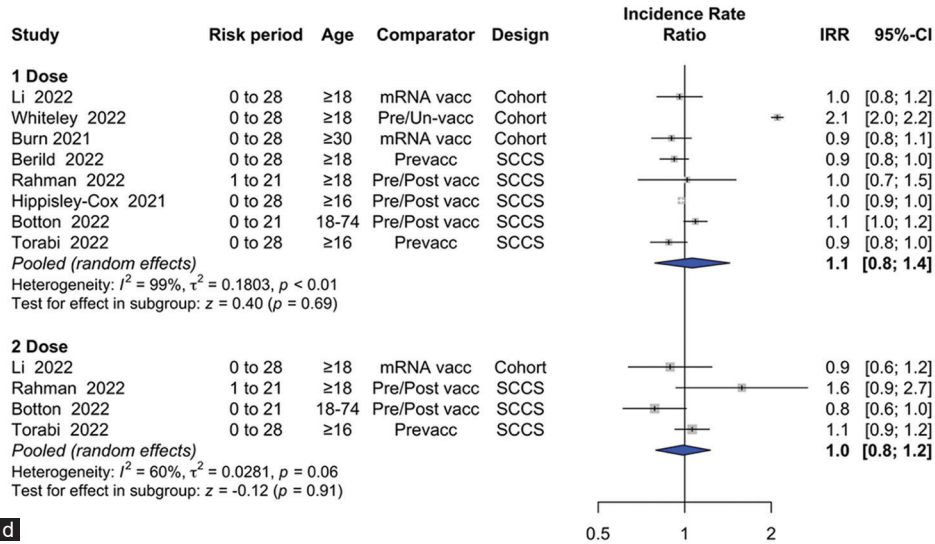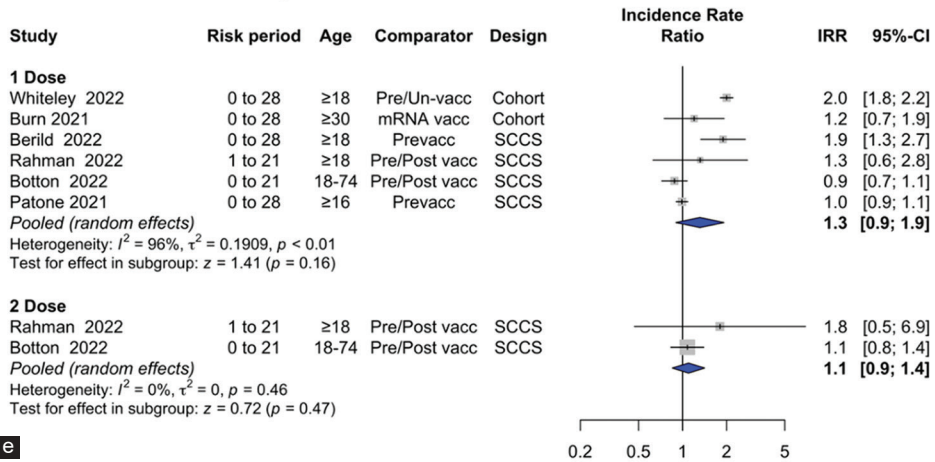| Study	Risk period	Age	Comparator	Design	IRR	95%-CI
1 Dose						
Li 2022	0 to 28	≥18	mRNA vacc	Cohort	1.3	[0.7; 2.3]
Vallone 2022	0 to 30	≥17	Influenza vacc	Cohort	10.5	[2.1; 52.1]
Whiteley 2022	0 to 28	≥18	Pre/Un-vacc	Cohort	2.1	[2.0; 2.2]
Burn 2021	0 to 28	≥30	mRNA vacc	Cohort	0.9	[0.8; 1.1]
Andrews 2022	0 to 27	≥15	Unvacc	Cohort	1.0	[1.0; 1.1]
Berild 2022	0 to 28	≥18	Prevacc	SCCS	1.8	[1.6; 2.1]
Rahman 2022	1 to 21	≥18	Pre/Post vacc	SCCS	2.5	[1.3; 4.9]
Simpson 2021	0 to 27	≥18	Prevacc	SCCS	1.0	[0.9; 1.2]
Hippisley-Cox 2021	0 to 28	≥16	Pre/Post vacc	SCCS	1.0	[0.9; 1.0]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	0.9	[0.8; 1.0]
Pooled (random effects)					**1.3**	**[1.0; 1.7]**

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.1554$, $p < 0.01$
Test for effect in subgroup: $z = 2.06$ ($p = 0.04$)

Study	Risk period	Age	Comparator	Design	IRR	95%-CI
2 Dose						
Li 2022	0 to 28	≥18	mRNA vacc	Cohort	0.8	[0.6; 1.1]
Simpson 2022	0 to 27	≥16	Pre/Post vacc	SCCS	0.8	[0.7; 1.0]
Rahman 2022	1 to 21	≥18	Pre/Post vacc	SCCS	1.2	[0.3; 4.7]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	0.9	[0.8; 1.0]
Pooled (random effects)					**0.9**	**[0.8; 1.0]**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$
Test for effect in subgroup: $z = -2.31$ ($p = 0.02$)

a

Any ATE

Incidence Rate Ratio

Study	Risk period	Age	Comparator	Design	IRR	95%-CI
1 Dose						
Li 2022	0 to 28	≥18	mRNA vacc	Cohort	0.9	[0.7; 1.0]
Whiteley 2022	0 to 28	≥18	Pre/Un-vacc	Cohort	2.2	[2.1; 2.3]
Berild 2022	0 to 28	≥18	Prevacc	SCCS	3.0	[1.7; 5.1]
Simpson 2021	0 to 27	≥18	Prevacc	SCCS	1.2	[1.1; 1.3]
Hippisley-Cox 2021	0 to 28	≥16	Pre/Post vacc	SCCS	1.0	[1.0; 1.0]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	1.0	[0.9; 1.0]
Pooled (random effects)					**1.3**	**[0.9; 1.9]**

Heterogeneity: $I^2 = 100\%$, $\tau^2 = 0.1902$, $p < 0.01$
Test for effect in subgroup: $z = 1.51$ ($p = 0.13$)

Study	Risk period	Age	Comparator	Design	IRR	95%-CI
2 Dose						
Li 2022	0 to 28	≥18	mRNA vacc	Cohort	1.0	[0.8; 1.3]
Simpson 2022	0 to 27	≥16	Pre/Post vacc	SCCS	0.9	[0.9; 1.0]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	1.0	[0.9; 1.1]
Pooled (random effects)					**1.0**	**[0.9; 1.0]**

Heterogeneity: $I^2 = 60\%$, $\tau^2 = 0.0025$, $p = 0.08$
Test for effect in subgroup: $z = -0.87$ ($p = 0.39$)

b

Any Hemorrhage

Incidence Rate Ratio

Study	Risk period	Age	Comparator	Design	IRR	95%-CI
1 Dose						
Simpson 2021	0 to 27	≥18	Prevacc	SCCS	1.5	[1.1; 2.0]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	0.9	[0.7; 1.0]
Patone 2021	0 to 28	≥16	Prevacc	SCCS	1.0	[0.9; 1.1]
Pooled (random effects)					**1.0**	**[0.8; 1.3]**

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.0341$, $p < 0.01$
Test for effect in subgroup: $z = 0.26$ ($p = 0.80$)

Study	Risk period	Age	Comparator	Design	IRR	95%-CI
2 Dose						
Simpson 2022	0 to 27	≥16	Pre/Post vacc	SCCS	0.8	[0.7; 1.0]
Torabi 2022	0 to 28	≥16	Prevacc	SCCS	1.0	[0.9; 1.2]
Pooled (random effects)					**0.9**	**[0.8; 1.1]**

Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.0147$, $p = 0.06$
Test for effect in subgroup: $z = -0.61$ ($p = 0.54$)

c

Supplemental Figure 2: Contd...

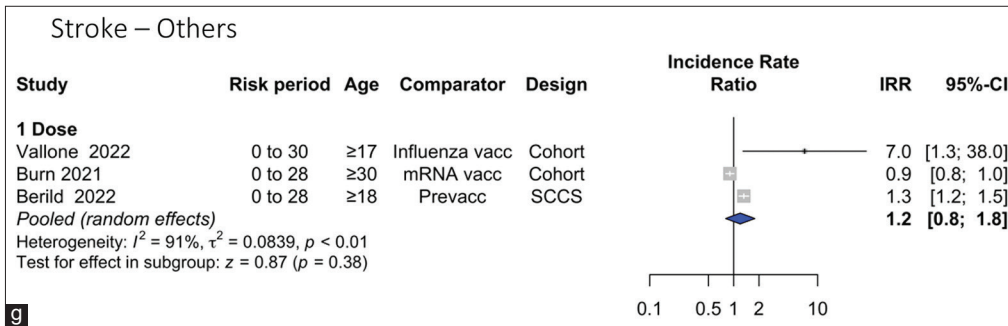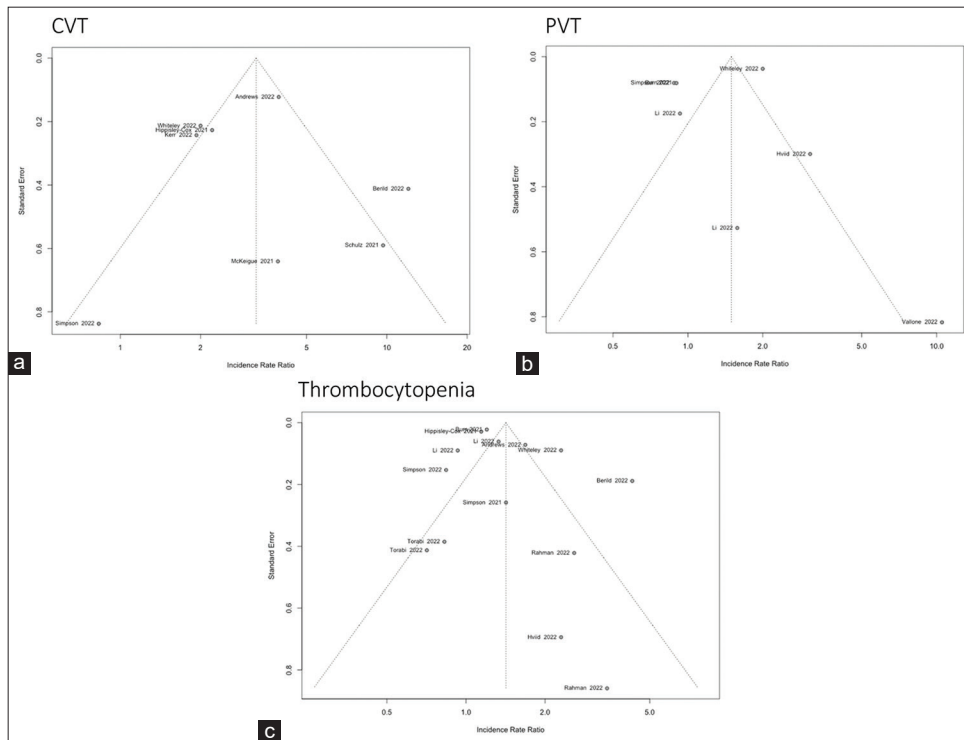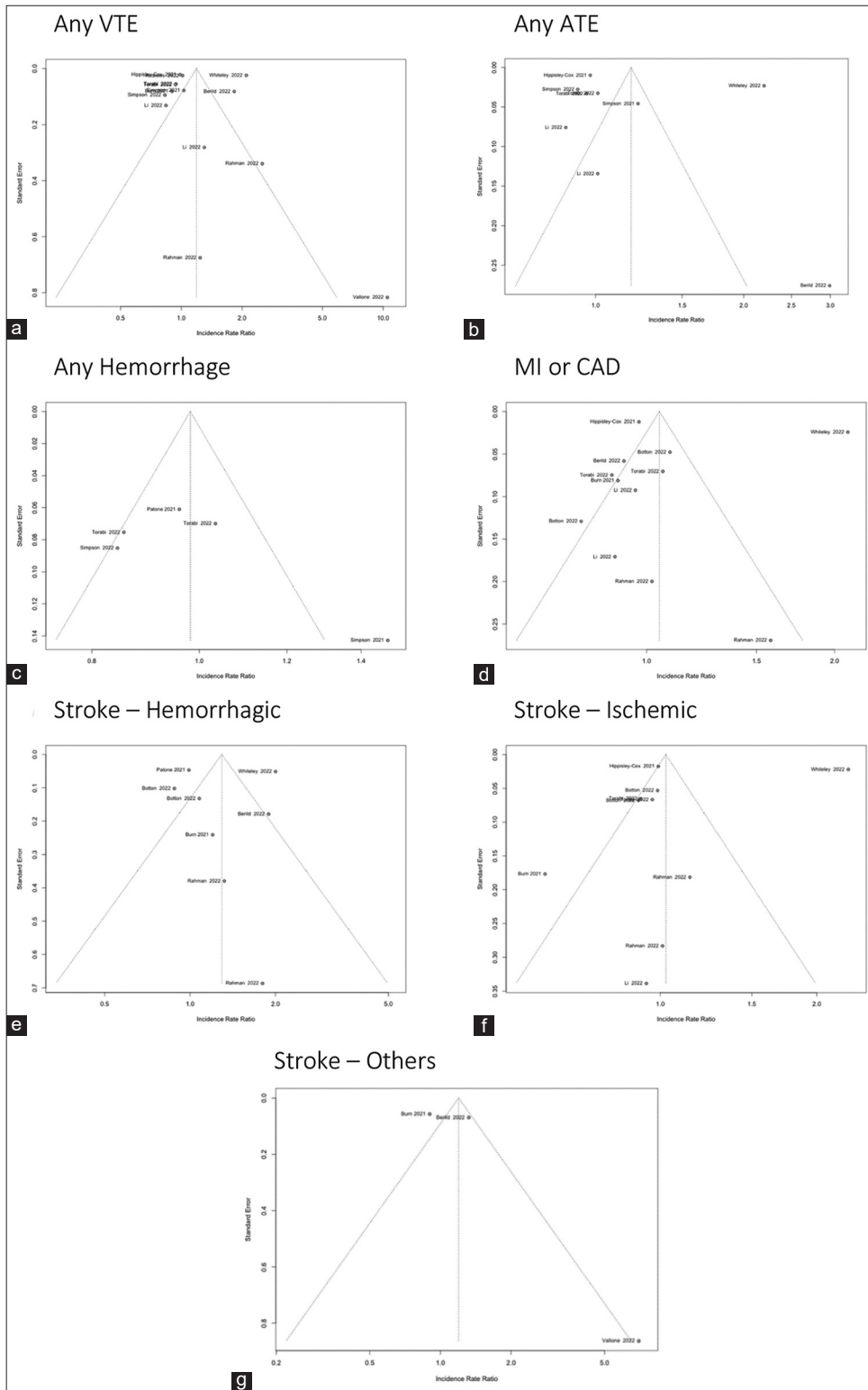**Supplemental Figure 2:** Contd...

Supplemental Figure 2: Forest plots showing pooled IRR for secondary outcomes by dose a) Any venous thromboembolism b) Any arterial thromboembolism c) Any hemorhage d) Myocardial infarction or Coronary artery disease e) Stroke- Hemorrhagic f) Stroke- Ischemic g) Stroke- Others

Supplemental Figure 3: Funnel plots for the primary outcomes a) Central venous thrombosis b) Peripheral venous thrombosis c) Thrombocytopenia

Supplemental Figure 4: Funnel plots for secondary outcomes a) Any venous thromboembolism b) Any arterial thromboembolism c) Any hemorhage d) Myocardial infarction or Coronary artery disease e) Stroke- Hemorrhagic f) Stroke- Ischemic g) Stroke- Others

Supplemental Table 1: GRADE approach for certainty of evidence for secondary outcomes

Outcomes	IRR (95% CI)	No of studies	Certainty of evidence (GRADE)	Comments
Any VTE after 1 dose	13 (1-17)	10 observational studies	Low	First dose of ChAdOx1 results in little to no difference in the risk of CVT.
Any VTE after 2 doses	09 (08-1)	4 observational study	Moderate	Second dose of ChAdOx1 likely results in little to no difference in any VTE
Any ATE after 1 dose	13 (09-19)	6 observational studies	Low	First dose of ChAdOx1 may result in little to no difference in any ATE
Any ATE after 2 doses	09 (09-1)	3 observational studies	Moderate	Second dose of ChAdOx1 likely results in little to no difference in any ATE
Any haemorrhage after 1 dose	1 (08-13)	3 observational studies	Very low	The evidence is very uncertain about the effect of first dose of ChAdOx1 on any haemorrhage.
Any haemorrhage after 2 doses	09 (08-11)	2 observational studies	Very low	The evidence is very uncertain about the effect of second dose of ChAdOx1 on any haemorrhage
MI or CAD after 1 dose	11 (08-14)	8 observational studies	Very low	The evidence is very uncertain about the effect of first dose of ChAdOx1 on any MI or CAD
MI or CAD after 2 doses	1 (08-12)	4 observational studies	Very low	The evidence is very uncertain about the effect of second dose of ChAdOx1 on any MI or CAD
Stroke- Haemorrhagic after 1 dose	13 (09-19)	6 observational studies	Low	First dose of ChAdOx1 may result in little to no difference in Stroke-Haemorrhagic
Stroke- Haemorrhagic after 1 dose	11 (09-14)	2 observational studies	Very low	The evidence is very uncertain about the effect of second dose of ChAdOx1 on Stroke- Haemorrhagic
Stroke- Ischemic after 1 dose	11 (07-16)	7 observational studies	Very low	The evidence is very uncertain about the effect of first dose of ChAdOx1 on Stroke-Ischemic
Stroke- Ischemic after 1 dose	09 (09-1)	3 observational studies	Very low	The evidence is very uncertain about the effect of second dose of ChAdOx1 on Stroke- Ischemic
Stroke- Others after 1 dose	12 (08-18)	3 observational studies	Very low	The evidence is very uncertain about the effect of first dose of ChAdOx1 on Stroke-Others

Supplemental Table 2: Risk of bias in the included studies

Table S1: Assessment of risk of bias of cohort studies using Newcastle-Ottawa quality assessment tool

Study	Domain wise stars*			Overall stars	Study quality**
	Selection	Comparability	Outcome		
Schulz 2021	2	1	2	5	Fair
Pottegard 2021	3	2	2	7	Good
Li 2022	3	2	2	7	Good
Vallone 2022	3	1	2	6	Fair
Andrews 2022	4	2	3	9	Good
Hviid 2022	3	1	2	6	Good
Whiteley 2022	3	2	2	7	Good
Burn 2021	4	1	3	8	Good
Sturkenboom 2022	3	1	3	7	Good

*Maximum 4 stars for selection domain; 2 stars for comparability domain and 3 stars for outcome domain. **Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain. Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain. Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain

Table S2: Assessment of risk of bias of SCCS studies using the modified Newcastle-Ottawa quality assessment tool

Study	Domain wise stars*			Overall stars	Study quality**
	Selection	Comparability	Outcome		
Simpson 2021	2	1	5	8	Good
McKeigue 2021	2	1	5	8	Good
Hippisley-Cox 2021	2	1	5	8	Good
Berild 2022	3	1	5	9	Good
Higgins 2022	3	1	5	9	Good
Rahman 2022	2	1	5	8	Good
Simpson 2022	2	1	5	8	Good
Kerr 2022	2	1	5	8	Good
Botton 2022	2	1	4	7	Good
Torabi 2022	2	1	5	8	Good
Patone 2021	2	1	5	8	Good

*Maximum 3 stars for selection domain; 2 stars for comparability domain and 5 stars for outcome domain. **Good quality: Overall 7-10 stars; Fair quality: Overall 4-6 stars; Poor quality: 3 stars and below