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Global Burden of Vaccine-Associated Cerebrovascular Venous Sinus Thrombosis, 1968–2024: A Critical Analysis From the WHO Global Pharmacovigilance Database

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ABSTRACT

Despite widespread coronavirus disease 2019 (COVID-19) vaccine use, research on the association between vaccines and cerebrovascular venous sinus thrombosis (CVST) in diverse populations is limited. This study aimed to address this gap. Data from the World Health Organization pharmacovigilance database (1968–2024; total reports = 8,909,484) were used. Reporting odds ratios (RORs) and information components (ICs) were calculated to assess the association between each drug and CVST. In total, 851 cases were identified as vaccine-associated CVST, of which 527 (61.93%) occurred in female patients. Only Ad5-vectored COVID-19 vaccines had the highest ROR and IC value with CVST (ROR, 4.78; 95% confidence interval, 4.34–5.28; IC, 2.15). The risk of CVST increased with age, with the 45–64-years age group having an IC of 1.35, while the 65 years and older group had a higher IC of 2.08. The findings highlight the need for clinicians to recognize the potential risks of CVST and prioritize rigorous monitoring and research to ensure patient safety.

Keywords: Cerebrovascular Venous Sinus Thrombosis; VigiBase; Epidemiology; Pharmacovigilance

Over the past century, vaccination programs have significantly reduced numerous life-threatening diseases, substantially improving global health outcomes.[1] This was especially evident during the coronavirus disease 2019 (COVID-19) pandemic, during which the rapid development of vaccines was crucial in controlling the spread.[2] However, while the benefits of vaccines are clear, it remains essential to continuously monitor potential adverse events

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Disclosure

The authors have no potential conflicts of interest to disclose.

Data Availability Statement

Data are available on reasonable request. Study protocol, statistical code: available from Dong Keon Yon (email: yonkkang@gmail.com). Data set: available from the Uppsala Monitoring Centre or World Health Organization through a data use agreement.

Author Contributions

Conceptualization: Cho J, Jo H, Kim H, Woo HG, Yon DK; Data curation: Cho J, Jo H, Kim H, Woo HG, Yon DK; Formal analysis: Cho J, Jo H, Kim H, Woo HG, Yon DK; Funding acquisition: Woo HG, Yon DK; Investigation: Cho J, Jo H, Kim H, Woo HG, Yon DK; Methodology: Cho J, Jo H, Kim H, Woo HG, Yon DK; Project administration: Cho J, Jo H, Kim H, Woo HG, Yon DK; Resources: Cho J, Jo H, Kim H, Woo HG, Yon DK; Software: Cho J, Jo H, Kim H, Woo HG, Yon DK; Supervision: Woo HG, Yon DK; Validation: Cho J, Jo H, Kim H, Woo HG, Yon DK; Visualization: Cho J, Jo H, Kim H, Woo HG, Yon DK; Writing - original draft: Cho J, Jo H, Kim H, Woo HG, Yon DK; Writing - review

to ensure vaccine safety. One rare but serious complication, particularly associated with COVID-19 vaccines, is cerebrovascular venous sinus thrombosis (CVST).[3] Despite its low incidence, the severity of CVST has raised concerns regarding vaccine safety in various populations. However, most studies have used regional datasets, limiting the generalizability of findings across different populations and healthcare systems.[4,5] Therefore, this study aims to analyze vaccine-associated CVST, specifically focusing on COVID-19 vaccines, using the large-scale global dataset from the World Health Organization (WHO).

VigiBase, the world's largest repository of individual case safety reports, is managed by the Uppsala Monitoring Centre (UMC) as part of the WHO Programme for International Drug Monitoring.[6] Established in 1968, VigiBase holds over 140 million reports of adverse drug reactions from over 170 countries. All CVST reports were reviewed, and vaccines with either no reported cases or an insufficient number of observations were consolidated into the "others" category to ensure statistical robustness and adequately represent underreported vaccines. Finally, data on vaccine-associated CVST were collected from 1968 to 2024 and classified into 8 groups: 1) diphtheria, tetanus toxoids, pertussis, polio, and *Hemophilus influenza* type b; 2) pneumococcal; 3) influenza; 4) papillomavirus; 5) COVID-19 mRNA; 6) Ad5-vectored COVID-19; 7) inactivated COVID-19 vaccines; and 8) others (anthrax, brucellosis, cholera, dengue virus, Ebola, encephalitis, enterovirus 7, hepatitis A, hepatitis B, leptospirosis, meningococcal, measles, mumps, rubella, monkeypox, plague, respiratory syncytial virus, rotavirus diarrhea, smallpox, tuberculosis, typhoid, yellow fever, and zoster vaccines). Adverse events were systematically deduplicated on a global scale using preferred terms from version 26.0 of the Medical Dictionary for Regulatory Activities (**Supplementary Tables 1** and **2**).[7] Additionally, key covariates, such as patient demographics (including age, sex, and region), characteristics of adverse events (reporting period, time to onset, and clinical outcome), and detailed vaccine information, were meticulously documented to facilitate a comprehensive analysis. All cases with unknown baseline characteristic values were excluded to minimize potential bias.

This study identified an association between different vaccines and the risk of CVST through disproportionality analysis, using two key measures: information component (IC) and reporting odds ratio (ROR).[8,9] A statistically significant association is observed when the lower limit of the 95% confidence interval (CI) for the IC ($IC_{0.25} > 0.00$) is positive, and both the ROR and its lower CI are greater than 1.00.[10] A two-sided P value < 0.05 was considered statistically significant. Additionally, we considered the results significant only when both analyses, with and without the exclusion of unknown values, demonstrated statistical significance. All analyses were performed using SAS (version 9.4; SAS Inc., Cary, NC, USA).

Initially, 4,258 cases of vaccine-associated CVST were identified. However, after excluding cases with unknown values, 851 vaccine-associated CVST cases were identified from 9,439 reports of all-cause CVST, of which 527 (61.93%) were reported in female patients (**Supplementary Table 3**). Among them, most of the cases were reported in Europe, followed by the Western Pacific region (**Fig. 1**). The majority of cases were reported in the working-age group (18–64 years; 81.19%) rather than youth (0–17 years; 2.12%). The number of reported cases remained low until 2020; however, it increased markedly in subsequent years (**Fig. 2**). After the introduction of COVID-19 vaccines in 2021, most reported cases of vaccine-associated CVST were linked to these vaccines (98.00%).

However, as presented in **Table 1**, the analysis of vaccine-associated CVST showed a significant association only with Ad5-vectored COVID-19 vaccines, with an ROR of 4.78

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(95% CI, 4.34–5.28) and an IC value of 2.15 ($IC_{0.25}$, 1.99). Interestingly, no association with CVST was observed for other vaccine types. However, COVID-19 mRNA vaccines showed a significant ROR of 1.13 (95% CI, 1.02–1.25), whereas the IC value did not indicate a significant association, with an estimate of 0.17 ($IC_{0.25}$, −0.01).

Moreover, although no deaths were reported, more than half of the vaccine-associated CVST cases (53.12%) resulted in nonrecovery or fatal outcomes (**Supplementary Table 4**). Among the reported cases, fatal outcomes were observed exclusively in individuals who received COVID-19 mRNA or Ad5-vectored COVID-19 vaccines, with the latter showing a significantly higher rate of fatal outcomes (30.4%) than the former (4.6%).

In our analysis, vaccine-associated CVST cases were significantly associated with Ad5-vectored COVID-19 vaccines. These findings may be explained by vaccine-induced immune thrombotic thrombocytopenia. This mechanism is well-known in adenoviral vector-based vaccines and aligns with our finding of the highest fatality rate in Ad5-vectored vaccine cases.[11]

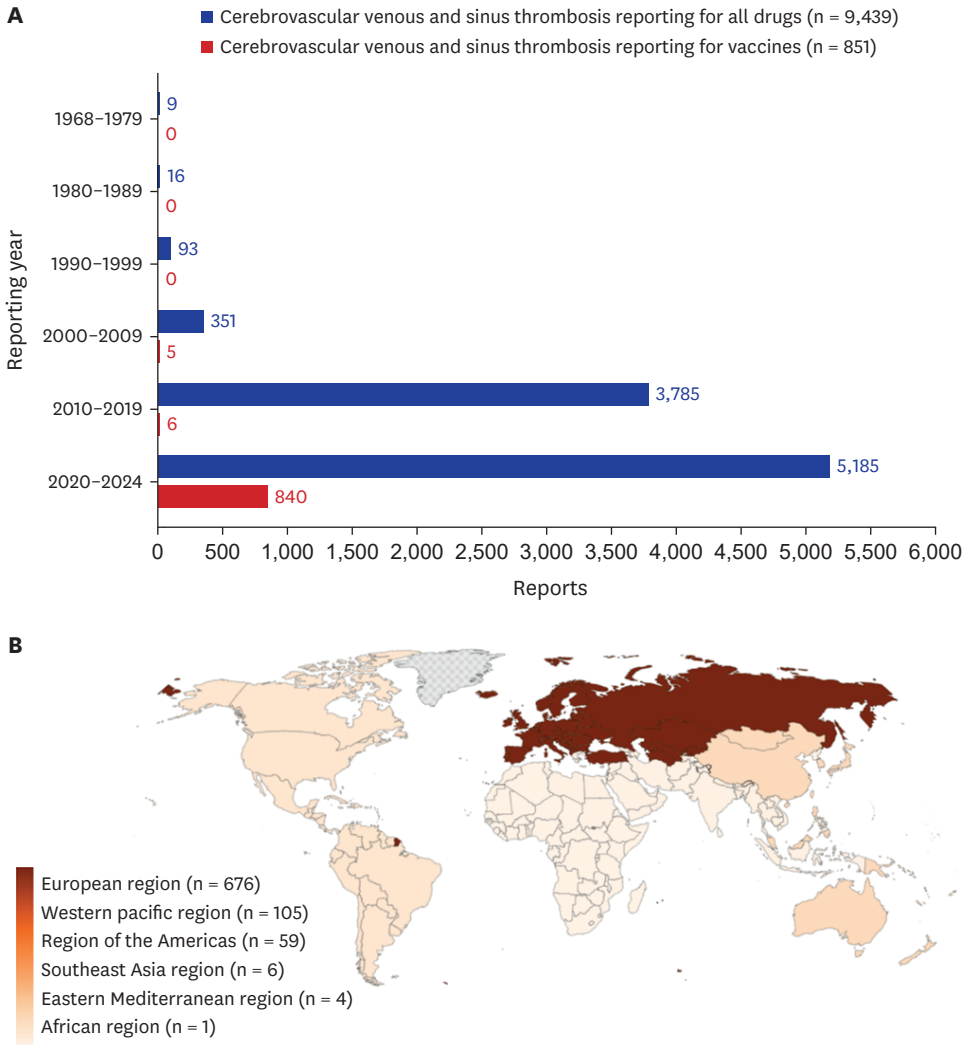

Fig. 1. Trends and global distribution of vaccine-associated cerebrovascular venous and sinus thrombosis. Temporal trends (**A**) and global distribution (**B**) of vaccine-associated cerebrovascular venous and sinus thrombosis adverse events by continent.

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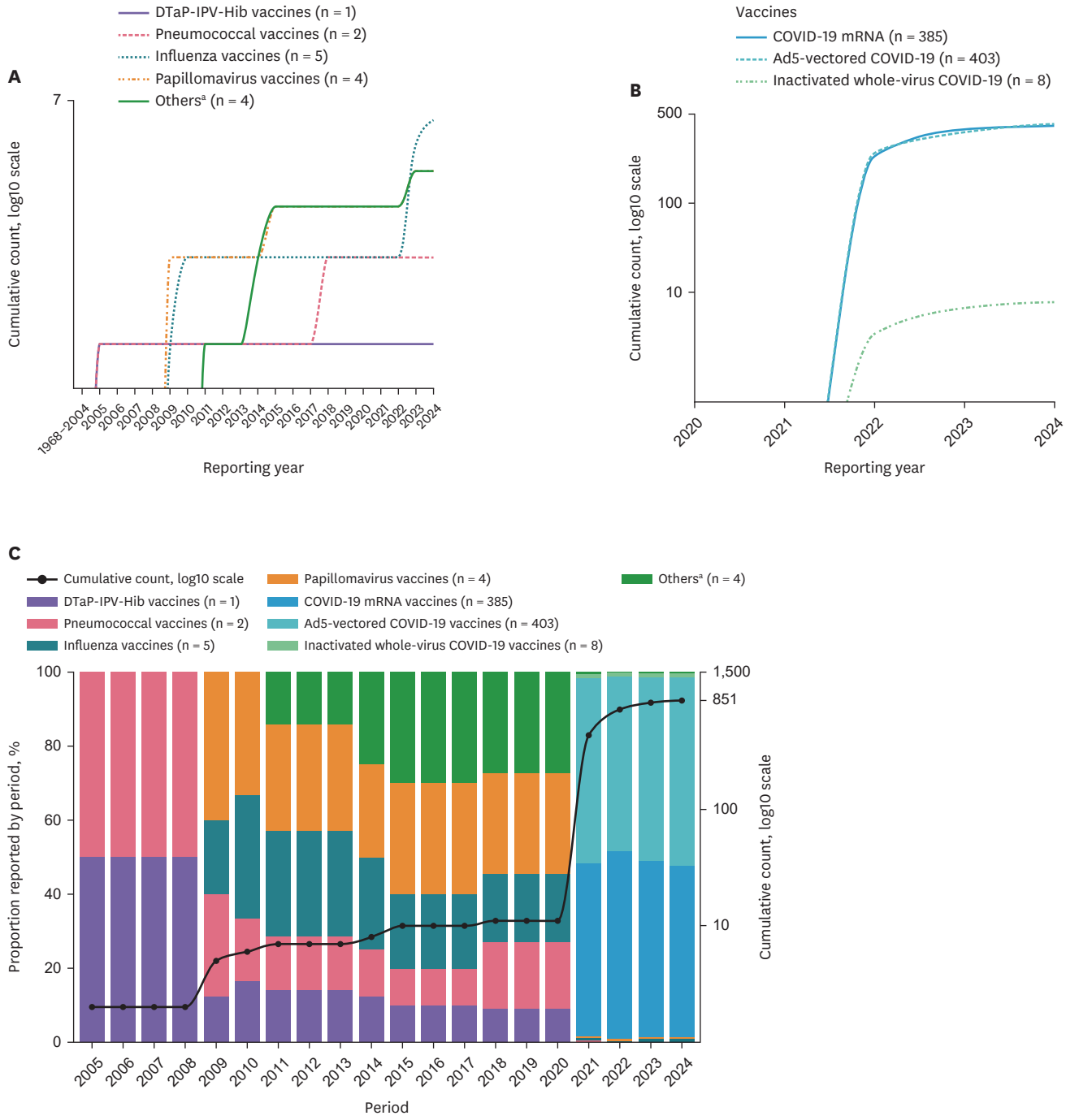

Fig. 2. Cumulative number of reports of cerebrovascular venous and sinus thrombosis adverse events per year in association with different vaccines. Temporal cumulative reports of vaccine-associated cerebrovascular venous and sinus thrombosis for overall vaccines (**A**) and COVID-19 vaccines (**B**), along with their distribution (**C**).
DTaP-IPV-Hib = diphtheria, tetanus toxoids, pertussis, polio, and *Hemophilus influenza* type b, COVID-19 = coronavirus disease 2019.
[a]Others: anthrax, brucellosis, cholera, dengue virus, Ebola, encephalitis, enterovirus 7, hepatitis A, hepatitis B, leptospirosis, meningococcal, measles, mumps, rubella, monkeypox, plague, respiratory syncytial virus, rotavirus diarrhea, smallpox, tuberculosis, typhoid, yellow fever, zoster vaccines.

This immune response induces a prothrombotic state in the cerebral venous sinuses, resulting in thrombocytopenia and promoting clot formation. Furthermore, individuals aged 45 years and older are already at an elevated risk of thrombosis due to endothelial

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Table 1. Analysis of subgroups in vaccine-associated cerebrovascular venous and sinus thrombosis adverse events disproportionality

Variables	Total	Vaccine-associated cerebrovascular venous and sinus thrombosis			IC ($IC_{0.25}$) based on age, yr				
		Observed	ROR (95% CI)	IC ($IC_{0.25}$)	0–11	12–17	18–44	45–64	≥ 65
Total	4,904,264	851	**1.41 (1.31–1.51)**	**0.46 (0.34)**	−3.80 (−5.22)	−2.37 (−3.35)	0.08 (−0.08)	**1.35 (1.16)**	**2.08 (1.80)**
Sex difference									
Male	1,933,895	324	**1.87 (1.66–2.10)**	**0.82 (0.63)**	−6.84 (−17.17)	−1.58 (−3.14)	**0.86 (0.58)**	**1.70 (1.40)**	**2.15 (1.72)**
Female	2,970,369	527	**1.24 (1.13–1.35)**	**0.28 (0.14)**	−2.34 (−3.76)	−2.75 (−4.05)	−0.19 (−0.39)	**1.13 (0.87)**	**2.01 (1.65)**
Vaccine types									
DTaP-IPV-Hib vaccines	710,623	1	0.01 (0.00–0.08)	−5.91 (−9.69)	N/A	N/A	−2.99 (−6.77)	N/A	N/A
Pneumococcal vaccines	207,988	2	0.08 (0.02–0.30)	−3.42 (−6.01)	−2.63 (−6.41)	N/A	−1.14 (−4.93)	N/A	N/A
Influenza vaccines	294,211	6	0.16 (0.07–0.36)	−2.53 (−3.95)	N/A	N/A	−2.52 (−4.59)	N/A	−0.08 (−2.15)
Papillomavirus vaccines	104,691	4	0.30 (0.11–0.81)	−1.61 (−3.37)	N/A	−3.44 (−7.22)	−0.86 (−2.92)	N/A	N/A
COVID-19 mRNA vaccines	2,098,107	392	**1.13 (1.02–1.25)**	0.17 (−0.01)	−0.42 (−3.02)	−0.89 (−1.91)	−0.15 (−0.39)	**0.66 (0.34)**	**1.92 (1.55)**
Ad5-vectored COVID-19 vaccines	583,806	434	**4.78 (4.34–5.28)**	**2.15 (1.99)**	1.25 (−2.53)	N/A	**1.38 (1.14)**	**3.13 (2.88)**	**3.84 (3.41)**
Inactivated whole virus vaccines	138,761	8	0.35 (0.17–0.69)	−1.47 (−2.69)	N/A	N/A	−1.86 (−3.42)	−0.37 (−2.44)	N/A
Others[a]	766,077	4	0.04 (0.02–0.11)	−4.43 (−6.20)	−3.63 (−6.22)	N/A	−3.79 (−6.39)	N/A	N/A

Bold style indicates when the value of $IC_{0.25}$ is greater than 0.00 or the lower end of the ROR 95% CI is greater than 1.00. This means it is statistically significant. Numbers in bold indicate a statistical significance.
ROR = reporting odds ratio, CI = confidence interval, IC = information component, DTaP-IPV-Hib = diphtheria, tetanus toxoids, pertussis, polio, and *Hemophilus influenza* type b, N/A = not available, COVID-19 = coronavirus disease 2019.
[a]Others: anthrax, brucellosis, cholera, dengue virus, Ebola, encephalitis, enterovirus 7, hepatitis A, hepatitis B, leptospirosis, meningococcal, measles, mumps, rubella, monkeypox, plague, respiratory syncytial virus, rotavirus diarrhea, smallpox, tuberculosis, typhoid, yellow fever, zoster vaccines.

dysfunction, heightened inflammatory responses, and various underlying conditions.[12] Vaccination may interact with these pre-existing factors, potentially increasing the risk of thrombotic events, which is consistent with and supports our findings.

Additionally, our findings align with restrictions placed on certain vaccines, particularly viral vector-based COVID-19 vaccines, owing to significant adverse events such as CVST.[13] Furthermore, the observed increase in CVST reports since 2020 cannot be attributed solely to COVID-19 vaccines, as it may also reflect enhanced pharmacovigilance efforts during the pandemic. Given these findings, careful administration of COVID-19 vaccines, particularly Ad5-vectored vaccines, is crucial, because CVST is a rare but serious condition. Furthermore, the importance of robust pharmacovigilance systems for monitoring and managing adverse CVST events has been strongly emphasized.[14]

However, this study has several limitations. First, VigiBase relies on spontaneous reporting, which may result in under- or over-reporting and reporting bias in case details. This is particularly evident in regions such as Africa, where adverse vaccine events may go unreported owing to limited access to medical services and lack of follow-up, resulting in lower reporting rates and potential gaps in epidemiological assessments. Furthermore, some time-to-onset values are reported in years, whereas others are reported in days, which may lead to potential misinterpretation. Second, owing to the observational nature of the data, establishing a direct causal link between vaccines and CVST is challenging. Therefore, these findings should be approached with caution and understood as statistical associations rather than as evidence of causation. Lastly, the two indicators used in this analysis, IC and ROR, can demonstrate the association between specific vaccines and their adverse events, but do not provide a measure of relative risk among different vaccine types.

Despite its limitations and the need for cautious interpretation, VigiBase offers valuable real-world, large-scale insights into vaccine-associated CVST across diverse populations.

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Its extensive dataset encompasses many patient demographics and clinical scenarios, including sex, ethnicity, and geographical region. This comprehensive coverage enables the identification of rare adverse events that may not be apparent in smaller, localized studies.[15]

Our study highlights a significant association between Ad5-vectored COVID-19 vaccines and CVST. Given the observed increase in CVST cases, it is imperative that clinicians acknowledge the potential risks of CVST associated with the administration of these vaccines. Additionally, rigorous monitoring and ongoing research into potential adverse reactions are essential to ensure patient safety.

Ethics statement

In primary data collection, as VigiBase is managed by the UMC, an independent organization, no ethics approval or Institutional Review Board number is issued by the UMC for VigiBase. For secondary analysis, the Institutional Review Board of Kyung Hee University Medical Center approved the use of the confidential, electronically processed population-level dataset (KHUH 2022-06-042). Owing to the population-level dataset, the ethics committee waived the requirement for written consent.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

MedDRA preferred terms for concurrent adverse reactions

Supplementary Table 2

MedDRA preferred terms and classifications for cerebrovascular venous and sinus thrombosis

Supplementary Table 3

Baseline characteristics of reports on vaccine-associated cerebrovascular venous and sinus thrombosis adverse events (N = 851)

Supplementary Table 4

Vaccine class-based description of adverse reactions (heatmap)

REFERENCES

1. Greenwood B. The contribution of vaccination to global health: past, present and future. *Philos Trans R Soc Lond B Biol Sci* 2014;369(1645):20130433. PUBMED | CROSSREF
2. Le TT, Cramer JP, Chen R, Mayhew S. Evolution of the COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 2020;19(10):667-8. PUBMED | CROSSREF

3. Hwang J, Park SH, Lee SW, Lee SB, Lee MH, Jeong GH, et al. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score. *Eur Heart J* 2021;42(39):4053-63. PUBMED | CROSSREF
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(22):2092-101. PUBMED | CROSSREF
5. Kehr S, Berg P, Müller S, Fiedler SA, Meyer B, Ruppert-Seipp G, et al. Long-term outcome of patients with vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis. *NPJ Vaccines* 2022;7(1):76. PUBMED | CROSSREF
6. Bataille P, Lebrun-Vignes B, Bettuzzi T, Ingen-Housz-Oro S, Hadj-Rabia S, Welfringer-Morin A, et al. Drugs associated with epidermal necrolysis in children: a World Health Organization pharmacovigilance database analysis. *J Eur Acad Dermatol Venereol* 2024;38(9):1791-8. PUBMED | CROSSREF
7. Stämpfli D, Dommrich R, Orbach-Zinger S, Burden AM, Heesen M. An explorative analysis of pharmacovigilance data of oxytocin and its analogue carbetocin, with a focus on haemodynamic adverse effects. *Int J Clin Pharm* 2023;45(4):922-8. PUBMED | CROSSREF
8. Cho H, Lee K, Jeong YD, Udeh R, Acharya KP, Kang J, et al. Global burden of ADHD medication-associated cardiovascular disease, 1967–2023: a comparative analysis using the WHO pharmacovigilance database. *Asian J Psychiatr* 2024;101:104209. PUBMED | CROSSREF
9. Yang JM, Jung SY, Kim MS, Lee SW, Yon DK, Shin JI, et al. Cardiovascular and cerebrovascular adverse events associated with intravitreal anti-VEGF monoclonal antibodies: a World Health Organization pharmacovigilance study. *Ophthalmology* 2025;132(1):62-78. PUBMED | CROSSREF
10. Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;19(12):1579-89. PUBMED | CROSSREF
11. Perry RJ, Tamborska A, Singh B, Craven B, Marigold R, Arthur-Farraj P, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. *Lancet* 2021;398(10306):1147-56. PUBMED | CROSSREF
12. Mastellos DC, Skendros P, Lambris JD. Is complement the culprit behind COVID-19 vaccine-related adverse reactions? *J Clin Invest* 2021;131(11):e151092. PUBMED | CROSSREF
13. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *JAMA* 2021;325(24):2448-56. PUBMED | CROSSREF
14. Lundstrom K, Barh D, Uhal BD, Takayama K, Aljabali AAA, Abd El-Aziz TM, et al. COVID-19 vaccines and thrombosis-roadblock or dead-end street? *Biomolecules* 2021;11(7):1020. PUBMED | CROSSREF
15. Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - a report of two UK cases. *Brain Behav Immun* 2021;95:514-7. PUBMED | CROSSREF