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TO THE EDITOR:

Cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia after a second ChAdOx1 nCoV-19 dose

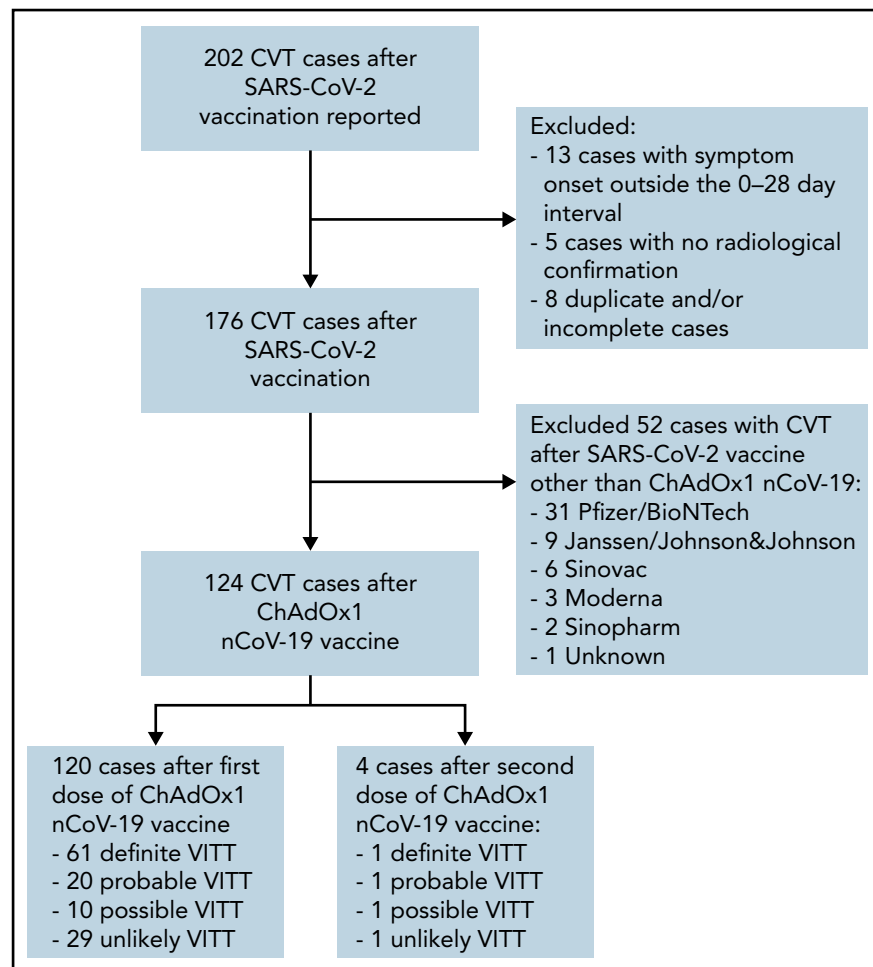
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Cerebral venous thrombosis (CVT) is the most common and severe manifestation of vaccine-induced immune thrombotic thrombocytopenia (TITT), which is a rare side effect of the SARS-CoV-2

vaccine ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca/Oxford).¹⁻⁴ The absolute risk of TITT and TITT-related CVT is estimated at 20 and 8 per million first doses of ChAdOx1 nCoV-19, respectively.^{5,6}

Figure 1. Flowchart of patient selection. Out of 202 reported patients with CVT after SARS-CoV-2 vaccination, we excluded 13, 5, and 8 cases with symptom onset outside of the 0-28 day interval, with no radiological confirmation, and duplicate and/or incomplete cases, respectively. Out of the remaining 176 cases, 124 cases developed CVT after ChAdOx1 nCoV-19 vaccination. Of these, 120 developed CVT after a first dose (61 definite, 20 probable, 10 possible, and 29 unlikely VITT), and 4 after a second dose (1 definite, 1 probable, 1 possible, and 1 unlikely).



So far, no definite VITT cases occurring after a second ChAdOx1 nCoV-19 vaccine dose have been reported, raising the question of whether VITT only occurs after a first dose. Two pharmacovigilance studies reported cases of thrombosis with thrombocytopenia after a second ChAdOx1 nCoV-19 dose, but because of lack of clinical data, none of these could be classified as VITT.⁷⁻⁹ Knowledge on whether VITT can occur after a second ChAdOx1 nCoV-19 dose is relevant for clinicians and policymakers, especially in low- and middle-income countries, which are currently the main users of adenovirus-based vaccines.¹⁰

We used data from the “CVT after SARS-CoV-2 vaccination” registry^{4,11} to identify VITT-related CVT cases occurring after a second ChAdOx1 nCoV-19 dose.

Details of this registry have been published.⁴ Briefly, this ongoing study collects data on patients with CVT with symptom onset ≤ 28 days from SARS-CoV-2 vaccination, regardless of the type and dose of vaccine. The study is endorsed by the European Academy of Neurology and the European Stroke Organization. Investigators are instructed to report consecutive cases from their hospitals. The ethical review board of the Academic

Medical Centre issued a waiver of formal approval for this observational study. Each center obtained local permission to carry out the study and acquired informed consent for the use of pseudonymized care data according to national law.

We used the case definition criteria of the United Kingdom expert hematology panel to classify cases as definite, probable, possible, or unlikely VITT after ChAdOx1 nCoV-19 administration among CVT cases reported until 1 December 2021.⁹

Within the study period, 202 CVT cases after SARS-CoV-2 vaccination were reported from 24 countries (Figure 1). Of the 124 patients with CVT following ChAdOx1 nCoV-19 vaccination, 120 were after a first dose, and 4 were after a second dose. There were 61 definite, 20 probable, 10 possible, and 29 unlikely VITT cases after a first ChAdOx1 nCoV-19 dose. Of the 4 cases after the second dose, 1 was definite, 1 was probable, 1 was possible, and 1 was an unlikely VITT. There were no possible, probable, or definite VITT cases after the second dose of any of the other vaccines.

Details of the 4 cases after a second ChAdOx1 nCoV-19 dose are provided in Table 1. A timeline of the clinical course of each of

Table 1. Clinical details of CVT cases after a second ChAdOx1 nCoV-19 dose

	Patient 1	Patient 2	Patient 3	Patient 4
VITT classification*	Probable	Definite	Possible	Unlikely
Demographics				
Age†	60s	50s	40s	60s
Sex	Male	Female	Male	Male
Medical history	Unremarkable	Thrombophilia	Unremarkable	Unremarkable
Prior COVID-19 infection at any time	No	No	No	No
Baseline characteristics				
Interval between first and second vaccination (d)‡	90	44	62	77
Interval between second vaccination and symptom onset (d)	5	6	1	4
Interval between symptom onset and diagnosis (d)	0	1	0	0
Headache	No	Yes	Yes	No
Focal neurologic deficits	Yes	Yes	Yes	Yes
Coma	Yes	Yes	No	No
Seizure	No	No	Yes	Yes
Imaging findings				
Intracerebral hemorrhage	Yes	Yes	No	No
Location of CVT	Superior sagittal sinus	Superior sagittal sinus, left transverse and sigmoid sinus, straight sinus, left jugular vein	Right transverse and sigmoid sinuses	Superior sagittal sinus, right transverse and sigmoid sinus, right jugular vein
Laboratory values				
Platelet count at admission, $\times 10^9/L$	188	40	109	175
Platelet count nadir, $\times 10^9/L$	55	14	55	124
Anti-PF4 antibody ELISA	Negative	Positive	Negative	Negative
Type ELISA test	Lifecodes PF4 IgG from Immucor	PF4 IgG from Immucor	Lifecodes PF4 IgG from Immucor	ZYMUTEST HIA IgG, HYPHEN BIOMED
Optical density ELISA	0.06	2.12§	0.12	0.03
Optical density test threshold	≥ 0.4	≥ 0.4	≥ 0.4	≥ 0.3
Functional assay to detect platelet-activating PF4 antibodies	Positive	Not performed	Positive	Negative¶
Type of functional assay	Modified HIPA	NA	Modified HIPA	Multiplate HIMEA
D-dimer, ug/L FEU	35 200	29 100	2400	513
Fibrinogen, g/L	4.17	2.63	3.34	4.14
	ref <3.50	ref <4.00	ref <3.50	ref <4.50

ELISA, enzyme-linked immunosorbent assay; FEU, fibrinogen equivalent units; HIMEA, heparin-induced multiple electrode aggregometry; HIPA, heparin-induced platelet aggregation; IVIG, intravenous immune globulin; NA, not applicable; VTE, venous thromboembolism.

*According to the United Kingdom expert hematology panel.⁹

†To avoid the possibility of patient identification, exact age has been removed.

‡In all cases, the first vaccination was ChAdOx1 nCoV-19.

§Blood was drawn from the patient at admission, stored at 4°C for 1 wk, then stored at -20°C for 327 d before it was tested.

||Modified HIPA assay was performed as previously described.¹⁵

¶HIMEA assay was performed as previously described.¹⁶

#Reason: multiple intracerebral hemorrhages and diffuse subarachnoid hemorrhage.

**Worsening of intracerebral hemorrhages.

Table 1. (continued)

	Patient 1	Patient 2	Patient 3	Patient 4
Treatment				
Anticoagulation	Argatroban	None [#]	Argatroban followed by dabigatran	Fondaparinux followed by dabigatran
IVIg	Yes	No	Yes	No
Decompressive hemicraniectomy	Yes	No	No	No
Complications and outcome				
Major bleeding during admission	Yes**	No	No	No
New VTE during admission	No	Yes, pelvic veins	No	No
Outcome at hospital discharge	Dead	Dead	No disability	No disability
Days between symptom onset and death	2	3	NA	NA
Cause of death	Brain herniation	Brain herniation	NA	NA

ELISA, enzyme-linked immunosorbent assay; FEU, fibrinogen equivalent units; HIMEA, heparin-induced multiple electrode aggregometry; HIPA, heparin-induced platelet aggregation; IVIG, intravenous immune globulin; NA, not applicable; VTE, venous thromboembolism.

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[#]Reason: multiple intracerebral hemorrhages and diffuse subarachnoid hemorrhage.

**Worsening of intracerebral hemorrhages.

the cases is provided in supplemental Figures 1-4, available on the *Blood* Web site. None of the patients reported any symptoms after the first dose of ChAdOx1 nCoV-19. The patients (3 men, 1 woman) were between their forties and sixties. None had preexistent comorbidities. The interval between receiving the second vaccine dose and symptom onset varied between 1 and 6 days. The 2 patients who met the criteria for probable and definite VITT (patients 1 and 2) both died of brain herniation.

In patient 3 with symptom onset on day 1, the rapid onset could be explained if circulating anti-PF4 antibodies were present after the first vaccination, suggesting immunological preconditioning similar to that described in heparin-induced thrombocytopenia.¹²

Of note, no specific events were observed after the first dose of this vaccine, suggesting that the development of VITT after the second dose of ChAdOx1 nCoV-19 cannot be predicted on clinical grounds. Although the numbers are small, the clinical severity appears comparable to CVT-VITT after a first ChAdOx1 nCoV-19 dose, as 2 patients had an intracerebral hemorrhage, 1 had a concurrent venous thrombosis, and 2 patients died during admission.^{4,5,13}

Based on reported CVT cases to the registry, VITT appears to be much less common after a second ChAdOx1 nCoV-19 dose than after a first. However, since many countries, especially in Europe, restricted the use of the ChAdOx1 nCoV-19 vaccine after the emergence of VITT, the lower frequency of reported VITT after a second dose could partly be explained by the fact that fewer people received a second dose of ChAdOx1 nCoV-19 than a first dose. Even so, data from the European Centre for Disease Prevention and Control

show that, until week 33 of 2021, 39 million first doses and 29 million second doses were administered in the European Economic Area.¹⁴ Therefore, this imbalance cannot fully explain the difference in the incidence of VITT. Still, due to the risk of reporting bias, data from our registry must be interpreted cautiously when concluding that VITT is much less common after a second than after a first dose.

In conclusion, CVT-VITT can occur after the second dose of the ChAdOx1 nCoV-19 vaccine but was reported less often than after a first vaccine dose. Symptom onset of VITT may be more rapid after a second than after a first dose, but the low number of cases precludes firm conclusions.

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K.K., A.v.d.M., and M.S.v.K. are PhD candidates at the University of Amsterdam. This work is submitted in partial fulfillment of the requirement for the doctoral degree.

Authorship

Contribution: D.A.d.S. and J.M.C. conceptualized the study; K.K., A.v.d.M., and M.S.v.K. provided data curation; K.K. and A.v.d.M. provided formal analysis; K.K., A.v.d.M., J.Z., F.J.B., G.F., T.K., B.P., J.A.K.H., and M.S.v.K. provided investigation for the study; M.A., J.M.F., D.A.d.S., and J.M.C. are responsible for methodization; K.K., A.v.d.M., M.S.v.K., M.R.H., D.A.d.S., and J.M.C. provided project administration; M.A., J.M.F., D.A.d.S., and J.M.C. provided resources;

D.A.d.S. and J.M.C. supervised the study; K.K. and A.v.d.M. contributed validation and visualization; K.K., D.A.d.S., and J.M.C. wrote the original draft of the manuscript; K.K., A.v.d.M., J.Z., F.J.B., G.F., T.K., B.P., M.S.v.K., J.A.K.H., M.A., M.R.H., J.M.F., D.A.d.S., and J.M.C. wrote, reviewed, and edited the manuscript; and K.K., A.v.d.M., and J.M.C. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest disclosure: M.R.H. has received grants from the Swiss Heart Foundation and Bangerter Foundation; travel support from Bayer; personal fees for data safety monitoring board or advisory board participation from Amgen; and is a member of the European Stroke Organisation Board of Directors and European Stroke Organisation Education Committee. M.A. has received personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Covidien, Daiichi Sankyo, Medtronic, Novartis, Sanofi, Pfizer, and Amgen; and grants from the Swiss National Science Foundation and Swiss Heart Foundation. J.A.K.H. has received grants from Baxalta as well as personal fees paid to her institution from Shire, Ablynx, Roche, Sobi, and the Swiss Federal Office of Public Health. J.M.F. has received personal fees from Boehringer Ingelheim, Bayer, and Daiichi Sankyo as well as grants from Bayer. D.A.d.S. has received travel support from Boehringer Ingelheim; speaker fees from Bayer; and personal fees for advisory board participation from AstraZeneca. J.M.C. has received grants paid to his institution from Boehringer Ingelheim and Bayer and payments paid to his institution for data safety monitoring board participation by Bayer. The remaining authors declare no competing financial interests.

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Footnotes

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The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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