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

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### Abstract:

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

## **Running head: CVT-VITT after a second ChAdOx1 nCoV-19 vaccine**

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A complete list of the members of the Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group appears in the “Appendix.”

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Cerebral venous thrombosis (CVT) is the most common and a severe manifestation of vaccine-induced immune thrombotic thrombocytopenia (VITT), which is a rare side effect of the SARS-CoV-2 vaccine ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca/Oxford).<sup>1-4</sup> The absolute risk of VITT and VITT-related CVT is estimated at 20 and 8 per million first doses of ChAdOx1 nCoV-19, respectively.<sup>5,6</sup>

So far, no definite VITT cases occurring after a second ChAdOx1 nCoV-19 vaccine dose have been reported, raising the question if 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.<sup>7-9</sup> Knowledge on whether VITT can occur after a second ChAdOx1 nCoV-19 dose is relevant for clinicians and policy makers, especially in low- and middle income countries, which are currently the main users of adenovirus-based vaccines.<sup>10</sup>

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

Details of this registry have been published.<sup>4</sup> Briefly, this ongoing study collects data on patients with CVT with symptom onset <28 days of SARS-CoV-2 vaccination, regardless of the type and dose of vaccine. The study is endorsed by the European Academy of Neurology and European Stroke Organisation. Investigators are instructed to report consecutive cases from their hospitals. The ethical review board of the Academic Medical Centre gave 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.<sup>9</sup> For original data, please contact [j.coutinho@amsterdamumc.nl](mailto:j.coutinho@amsterdamumc.nl).

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 four 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 four cases after the second dose, one was definite, one was probable, one was possible, and one was an unlikely VITT. There were no possible, probable or definite VITT cases after a second dose of any of the other vaccines.

Details of the four cases after a second ChAdOx1 nCoV-19 dose are provided in Table 1. A timeline of the clinical course of each of the cases is provided in Supplemental Figures 1-4. None of the patients reported any symptoms after the first dose of ChAdOx1 nCoV-19. The patients – three men, one woman – were between their forties and sixties. None had pre-existent comorbidities. The interval between receiving the second vaccination dose and symptom onset varied between 1 and 6 days. The two patients who met the criteria for probable and definite VITT (no. 1 and 2) both died from 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.<sup>12</sup>

Of note, no specific events were observed after the first dose of this vaccine, suggesting that 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 two patients had intracerebral hemorrhage, one had a concurrent venous thrombosis and two patients died during admission.<sup>4,5,13</sup>

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 less 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.<sup>14</sup> Therefore, this imbalance cannot fully explain the difference in 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 a second dose of 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.M. and M.S.K. are PhD candidates at the University of Amsterdam. This work is submitted in partial fulfillment of the requirement for the PhD.

## **Authorship Contributions**

Contribution: Conceptualization: D.A.S. and J.M.C.; Data curation: K.K., A.M., and M.S.K.; Formal analysis: K.K. and A.M.; Investigation: K.K., A.M., J.Z., F.J.B., G.F., T.K., B.P., J.A.K.H, and M.S.K.; Methodology: M.A., J.M.F., D.A.S., and J.M.C.; Project administration: K.K., A.M., M.S.K., M.R.H., D.A.S., and J.M.C.; Resources: M.A., J.M.F., D.A.S., and J.M.C.; Supervision: D.A.S. and J.M.C.; Validation and visualization: K.K. and A.M.; Writing, original draft: K.K., D.A.S., and J.M.C.; Writing, review & editing: K.K., A.M., J.Z., F.J.B., G.F., T.K., B.P., M.S.K., J.A.K.H., M.A., M.R.H., J.M.F., D.A.S., J.M.C.

K.K., A.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

## **Disclosure of Conflicts of Interest**

Conflict-of-interest disclosure: K.K., A.M., J.Z., F.B., G.F., T.K., B.P. and M.S.K. have nothing to disclose. 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



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## Tables

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

	<b>Patient 1</b>	<b>Patient 2</b>	<b>Patient 3</b>	<b>Patient 4</b>
<b>VITT classification*</b>	Probable	Definite	Possible	Unlikely
<b>Demographics</b>				
<b>Age<sup>†</sup></b>	60s	50s	40s	60s
<b>Sex</b>	Male	Female	Male	Male
<b>Medical history</b>	Unremarkable	Thrombophilia	Unremarkable	Unremarkable
<b>Prior COVID-19 infection at any time</b>	No	No	No	No
<b>Baseline characteristics</b>				
<b>Interval between first and second vaccination, days<sup>‡</sup></b>	90	44	62	77
<b>Interval between second vaccination and symptom onset, days</b>	5	6	1	4
<b>Interval between symptom onset and diagnosis, days</b>	0	1	0	0
<b>Headache</b>	No	Yes	Yes	No
<b>Focal neurologic deficits</b>	Yes	Yes	Yes	Yes
<b>Coma</b>	Yes	Yes	No	No
<b>Seizure</b>	No	No	Yes	Yes

<b>Imaging findings</b>				
<b>Intracerebral hemorrhage</b>	Yes	Yes	No	No
<b>Location of CVT</b>	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
<b>Laboratory values</b>				
<b>Platelet count at admission, <math>\times 10^9/L</math></b>	188	40	109	175
<b>Platelet count nadir, <math>\times 10^9/L</math></b>	55	14	55	124
<b>Anti-PF4- antibody ELISA</b>	Negative	Positive	Negative	Negative
<b>Type ELISA test</b>	Lifecodes PF4 IgG from Immucor	PF4 IgG from Immucor	Lifecodes PF4 IgG from Immucor	ZYMUTEST™ HIA IgG, HYPHEN BIOMED
<b>Optical Density ELISA</b>	0.06	2.12 <sup>s</sup>	0.12	0.03
<b>Optical Density test threshold</b>	≥0,4	≥0.4	≥0,4	≥0,3
<b>Functional assay to detect platelet-activating PF4 antibodies</b>	Positive <sup>ll</sup>	Not performed	Positive <sup>ll</sup>	Negative <sup>ll</sup>

				Multiplate®
<b>Type of functional assay</b>	Modified heparin-induced platelet aggregation (HIPA)	NA	Modified heparin-induced platelet aggregation (HIPA)	Heparin-induced Multiple Electrode Aggregometry (HIMEA)
<b>D-dimer, ug/L FEU</b>	35200	29100	2400	513
<b>Fibrinogen, g/L</b>	4.17 (ref. <3.50)	2.63 (ref <4.00)	3.34 (ref<3.50)	4.14 (ref<4.50)
<b>Treatment</b>				
<b>Anticoagulation</b>	Argatroban	None <sup>#</sup>	Argatroban followed by dabigatran	Fondaparinux followed by dabigatran
<b>IVIG</b>	Yes	No	Yes	No
<b>Decompressive hemicraniectomy</b>	Yes	No	No	No
<b>Complications and outcome</b>				
<b>Major bleeding during admission</b>	Yes**	No	No	No
<b>New VTE during admission</b>	No	Yes, pelvic veins	No	No
<b>Outcome at hospital discharge</b>	Dead	Dead	No disability	No disability
<b>Days between symptom onset and death</b>	2	3	NA	NA
<b>Cause of death</b>	Brain herniation	Brain herniation	NA	NA

ELISA indicates enzyme-linked immunoassay; FEU, fibrinogen equivalent units; IVIG, intravenous immune globulin; NA, not applicable; and VTE, venous thromboembolism.

\* According to the United Kingdom expert hematology panel.<sup>9</sup>

† 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 patient at admission, stored at 4°C for 1 week, then stored at -20°C for 327 days before it was tested.

|| Modified HIPA assay was performed as previously described.<sup>15</sup>

¶ HIMEA assay was performed as previously described.<sup>16</sup>

# Reason: multiple intracerebral hemorrhages and diffuse subarachnoid hemorrhage.

\*\* Worsening of intracerebral hemorrhages.

## Figure Legends

**Figure 1. Flowchart of patient selection.** Out of 202 patients with CVT after SARS-CoV-2 vaccination reported, we excluded 13, 5 and 8 cases because of symptom onset outside of 0-28 day interval, no radiological confirmation, and duplicate and/or incomplete cases, respectively. Out of 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).

## Figures

**Figure 1. Flowchart of patient selection.**



