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Perry, RJ, Tamborska, A, Singh, B et al. (73 more authors) (2021) Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. The Lancet, 398 (10306). pp. 1147-1156. ISSN 0140-6736

https://doi.org/10.1016/s0140-6736(21)01608-1

Cerebral venous thrombosis following vaccination against COVID-19 in the UK: a multicentre cohort study

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Word count

Abstract: 311 words

Main text: 3862 words

Research in context

Evidence before this study

We searched PubMed on 26th May 2021 for articles published in 2021 with titles containing any of the following three search terms or their synonyms: thrombosis, platelet, PF4; together with any of the following: ChAdOx, AstraZeneca, Vaxzevria, Ad26.COV2.S, Janssen, Johnson, mRNA-1273, Moderna, BNT162b2, Pfizer, Comirnaty, COVID vaccine or SARS vaccine. 63 articles were found, of which 29 were case reports or small case series (nine focused specifically on cerebral venous sinus thrombosis), six were summaries of drug side-effect reports submitted to surveillance agencies, six were consensus statements regarding guidelines for diagnosis or management, 19 were reviews, commentaries or editorials and three were relevant immunological studies in normal subjects who had been vaccinated. Most case reports and small series were of vaccine-induced thrombotic thrombocytopenia (VITT) following vaccination with the adenovirus vector vaccine ChAdOx1 (AstraZeneca), with the typical features of very low platelets, very high D-dimers and most commonly cerebral venous sinus thrombosis or hepatic portal vein thrombosis. A similar syndrome has been reported following another adenovirus vector vaccine Ad26.COV2.S (Janssen/Johnson & Johnson). In both cases anti-PF4 antibodies were found in the majority of patients. The mRNA-based vaccines produced by Moderna (mRNA-1273) and Pfizer (BNT162b2) have also been associated with a syndrome of profound thrombocytopenia, but in this case the phenotype was typically idiopathic thrombocytopenic purpura (ITP), with a purpuric rash and mucosal bleeding as the most typical features. Although there have been occasional reports of thrombosis following mRNA vaccines, these did not have the characteristics of VITT and were probably incidental. Although cerebral venous thrombosis is the most severe manifestation of VITT, to date there have been no large studies focusing on this condition, and none of the reports so far have included a control group, which makes it difficult to draw inferences about how this condition differs from cerebral venous thrombosis without VITT.

Added value of this study

Our study provides the largest study of cerebral venous thrombosis following vaccination against COVID-19. We are able to make the first direct comparison between 70 patients with VITT-associated cerebral venous thrombosis and 25 patients who developed cerebral venous thrombosis following vaccination but did not have VITT, in addition to secondary comparisons with a large historical cerebral venous thrombosis cohort. Our results demonstrate for the first time that, compared with those without VITT, patients with VITT-associated cerebral venous thrombosis are younger, have fewer venous thrombosis risk factors and are more likely to have been given the ChAdOx1 vaccine. They develop more extensive cerebral venous thrombosis with more veins or sinuses thrombosed, and multiple intracerebral haemorrhage is more common. They are more likely to have concurrent

extracranial venous or arterial thromboses. Their outcomes at the end of hospital admission are worse, with higher rates of death and disability. Although the response of patients with VITT-associated cerebral venous thrombosis to treatment is difficult to assess in a purely observational study, non-heparin anticoagulants and intravenous immunoglobulin are both associated with a better outcome. The starting criteria for VITT, based on low platelets and high D-dimers, appeared to miss two patients who had typical features for this condition.

Implications of all the available evidence

VITT has a specific association with adenovector-based vaccines against COVID-19 and urgent work is needed to elucidate the trigger for this reaction, in the hope that future vaccines can be designed to avoid it. Clinicians need to be aware of the clinical, laboratory and radiological markers of this condition, as without prompt treatment the outcome is very poor. Adoption of the new definition of VITT-associated cerebral venous thrombosis that we have proposed should make it less likely that atypical cases will be missed, but these diagnostic criteria will need to be tested as more data accumulates.

Abstract

Background

A new syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side-effect of vaccination against COVID-19. Cerebral venous thrombosis is its most common manifestation but has not previously been described in detail. Our objectives were to document the features of post-vaccination cerebral venous thrombosis with and without VITT and to assess whether VITT is associated with a worse outcome.

Methods

We collected clinical characteristics, laboratory results and radiological features on admission of patients with cerebral venous thrombosis following vaccination against COVID-19, with no exclusion criteria. We compared the VITT and non-VITT groups for the proportion of patients who were dead or dependent at the end of admission.

Findings

The study included 95 patients with cerebral venous thrombosis following vaccination against COVID-19, from 43 UK hospitals. 70 had VITT and 25 did not. The median age in years of the VITT group (47, IQR 23) was lower than in the non-VITT group (57, IQR 21, p=0.0045).

Patients with VITT-associated cerebral venous thrombosis had more intracranial veins thrombosed (median 3, IQR 2) than non-VITT patients (median 2, IQR 1, p=0.041) and they more frequently had extracranial thrombosis (31/70, 44%) than non-VITT patients (1/25, 4%, p=0.0003).

The primary outcome of death or dependency occurred more frequently in VITT-associated cerebral venous thrombosis (33/70, 47%) than in the non-VITT control group (4/25, 13%, p=0.0061). This adverse outcome was less frequent in VITT patients who received non-heparin anticoagulation (18/50, 36%) than in those who did not (15/20, 75%, p=0.0031) and in those who received intravenous immunoglobulin (22/55, 40%) than in those who did not (11/15, 73%, p=0.022).

Interpretation

Cerebral venous thrombosis is more severe in the context of VITT. Non-heparin anticoagulants and immunoglobulin may improve outcome of VITT-associated cerebral venous thrombosis. Because the current definition excluded some patients with otherwise typical VITT-associated cerebral venous thrombosis, we propose new diagnostic criteria.

Funding

No funding.

Introduction

Globally over 3.4 million people have died from COVID-19[1]. In response to this public health emergency, several vaccines against COVID-19 have been developed, with more than 1.4 billion doses administered worldwide[1]. Following the introduction of the adenovirus-vector vaccine ChAdOx1 (Oxford-AstraZeneca), five cases of severe venous thrombosis with thrombocytopenia were reported in Norway, each starting 7-10 days after administration of the first dose. Of these, four had cerebral venous sinus thrombosis[2]. The syndrome has since been termed vaccine-induced immune thrombotic thrombocytopenia (VITT)[2,4]. A similar condition has been described with another adenovirus-based vaccine, Ad26.COV2.S (Johnson & Johnson)[5,6]. There are also case reports in which two mRNA vaccines, mRNA-1273 (Moderna)[7,8] and BNT162b2 (BioNtech-Pfizer)[9], are associated with thrombocytopenia, although typically with purpura and mucosal bleeding[7-10] rather than thrombosis[10].

Scully and colleagues[3] proposed the following definition for VITT: patients presenting with acute thrombosis and thrombocytopenia with elevated D-dimers, using a D-dimer threshold of <2000 μg/L for "VITT unlikely" and >4000 μg/L for "VITT suspected". They demonstrated that 22 out of 23 patients with VITT (96%) had antibodies against platelet factor 4 (PF4). Similar observations were made in other smaller case series[2,4].

Our objectives were to document the clinical features, laboratory and imaging results, and outcomes in a large cohort of VITT-associated cerebral venous thrombosis, and to compare these with patients with cerebral venous thrombosis but without VITT, and also with historical data from the 624 patients in the International Study on Cerebral Venous Vein and Dural Sinus Thrombosis (ISCVT) cohort[11].

Methods

Study design and participants

Clinicians involved in the care of these patients were identified through existing networks of communication among UK doctors, advertisement through UK neurology and stroke organisations, and via reports submitted to the UK Medicines and Healthcare products Regulatory Agency (MHRA). Clinicians were asked to submit all cases in which COVID-19 vaccination preceded the onset of cerebral venous thrombosis, regardless of the type of vaccine, interval between vaccine and onset of cerebral venous thrombosis symptoms, or blood results. There were no exclusion criteria. They were also encouraged to report their cases to the MHRA, the UK Expert Haematology Panel and Public Health

England, so data from those sources will include most of our cases. There was a combination of retrospective and prospective collection of cases.

Data were extracted from clinical notes, discharge summaries, results systems and radiology reports, by consultants (56 patients), specialist trainees (29 patients), other clinicians involved in the patients' care (4 patients) or trained stroke research practitioners (6 patients). We included details of exposure to COVID-19 vaccines, for a case-control comparison between cerebral venous thrombosis patients with and without VITT. For a cohort study following these two groups through their admission, we collected baseline demographics, venous thrombosis risk factors (including cerebral venous thrombosis risk factors identified in ISCVT[11]), clinical features, laboratory results, radiological findings and treatments given, with death or dependency (modified Rankin score[12] = 3-6) at the end of hospital admission as the primary outcome. Data were checked centrally for omissions, duplications or inconsistencies and data queries were sent back to the submitting clinicians until these were resolved. Case Report Forms were received between 1st April 2021 to 20th May 2021. The UK Health Research Authority confirmed that this surveillance study could proceed using anonymised patient data without patient consent.

Defining VITT-associated cerebral venous thrombosis

We defined cerebral venous thrombosis cases as VITT-associated if: 1. the lowest platelet count recorded during admission was below 150 $x10^9$/L and 2. if the D-dimer was measured, the highest value recorded was greater than 2000 μg/L, the lower of the two thresholds suggested by Scully and colleagues[3]. These are referred to as the "starting criteria" (different from the proposed criteria in the Panel). Before proceeding with any comparisons between groups, we first examined the frequency distributions of the minimum platelet count and maximum D-dimers recorded during admission across the whole study population, to confirm the appropriateness of these diagnostic thresholds in a population of patients with cerebral venous thrombosis.

We then compared the characteristics of patients with VITT-associated cerebral venous thrombosis with the patients in our own study who did not satisfy our starting criteria for VITT. The VITT group was also compared with the historical ISCVT cohort[11].

Statistical methods

Categorical variables were compared between groups using chi-squared tests, unless the expected number of patients in any one category was less than 5, in which case Fisher's exact test was used. The age distribution of VITT-associated cerebral venous thrombosis was compared with a single value

representing the median age of patients in the ISCVT collection[11], using the one-sample Wilcoxon signed rank test. All other continuous variables were compared using the Mann-Whitney U test.

The frequency of cases submitted was calculated for each five year interval between the ages of 15 and 70 years. The frequency was then also corrected for the number of patients vaccinated in each age group, this time using a bin width of 10 years to match with the national data from OpenSafely[13].

Results

Patients included

We received data on 99 patients from collaborators in 43 hospitals across the UK. Four patients were excluded because they did not have definitive evidence of cerebral venous thrombosis on imaging (Supplementary Figure S1). In 83/95 patients (87%) the modality on which cerebral venous thrombosis was demonstrated was CT venography, as illustrated in Figure 1. The lowest platelet count during admission was available for all 95 patients and the highest D-dimer was available in 62/70 patients with VITT (89%) and 20/25 patients without VITT (80%).

Anti-PF4 tests

76/95 patients (80%) were investigated for anti-PF4 antibodies on one or more anti-PF4 antibody tests. 74 were tested on at least one enzyme-linked immunosorbent assay (ELISA, Stago Asserachrom, Immucor Lifecodes or Hyphen Zymutest). 17 of these were additionally tested on an automated chemiluminescent HIT assay (Acustar HIT-IgG Assay), of whom 9 were positive on ELISA but negative on Acustar. No patients were positive on Acustar and negative on ELISA (Supplementary Materials Table S1). Six patients were tested on a flow cytometry platelet activation assay (Diapharma HITAlert Assay) and one patient on a gel agglutination assay (Diamed ID-PaGIA Heparin/PF4 Antibody Test).

Frequency distributions of platelet counts and D-dimers

We examined the whole study population for evidence from their platelet counts and D-dimers that there might be two sub-groups, postulated to be those with and without VITT. Histograms for the lowest platelet count recorded and the highest D-dimer recorded are shown in Figure 2. Given existing evidence that anti-PF4 antibodies are a reliable diagnostic marker for VITT[24], we also classified patients by anti-PF4 status: positive on any test (shown in red), negative in all tests used always including at least one ELISA test (blue) or not tested (grey).

Figure 2A shows the distribution of platelet counts, which supports the hypothesis that there is a distinct sub-group of patients with counts below 150 $x10^9$/L who, when tested, tended to be positive

for anti-PF4 antibodies, as predicted for the VITT group. However, one patient with evidence of anti-PF4 antibodies on two ELISA assays (Stago Asserachrom and Immucor Lifecodes) had a lowest platelet count of 158 $x10^9$/L (Patient B, Table S2, Supplementary Materials).

Among the 75 patients found to be thrombocytopenic on their lowest platelet count, seven were negative for anti-PF4 antibodies on ELISA tests. Two of these patients satisfied the starting criteria for VITT with thrombocytopenia and peak D-dimers > 2000 μg/L but were negative on two different ELISA assays (Stago Asserachrom and Hyphen Zymutest, Patients E and F, Table S2, Supplementary Materials).

The histogram for the highest D-dimer is shown plotted on a logarithmic scale in Figure 2B. The distribution was bimodal. The value separating the two "empty" bars near the centre of the chart, the lower of which is labelled 1585, was $\log_{10}$(D-dimer) = 3.3, equivalent to D-dimer = 1995 μg/L. The distribution therefore supports the incorporation of a D-dimer threshold of 2000 μg/L into the criteria for diagnosing VITT-associated cerebral venous thrombosis.

Interval from vaccine date to cerebral venous thrombosis onset

The median interval between vaccination and cerebral venous thrombosis symptom onset was 9 days in patients with VITT and 11 days in those without VITT, which was not a significant difference (Figure S2 and Table 1). One patient with VITT developed clumsiness of his left arm 40 days after his first and only dose of ChAdOx1 vaccine, the first manifestation of a cortical vein thrombosis. However, he had developed a deep vein thrombosis, his first manifestation of VITT, 21 days after vaccination. The deep vein thrombosis was initially treated with tinzaparin, but he was found to be thrombocytopenic before this treatment. He was the only patient in the whole study to receive any form of heparin within the two weeks preceding the cerebral venous thrombosis.

Age distribution

The age distribution of patients with VITT-associated cerebral venous thrombosis (Supplementary Materials, Figure S3A) showed an abrupt increase in the frequency of cases above the age of 45 years, in keeping with the UK COVID-19 vaccination strategy. Our patients were all vaccinated on or before 30th April 2021 and prior to this date most individuals vaccinated in the UK were aged 45 years or more (see Supplementary Materials). When adjusted for the UK rate of vaccination per age group, using data from OpenSAFELY[13], the step-change in frequency above age 45 years was no longer apparent (Figure S3B).

Admission characteristics

Table 1 shows a comparison between the 70 cases with VITT-associated cerebral venous thrombosis and the 25 patients in our study who developed cerebral venous thrombosis without evidence of VITT following vaccination, as well as historical data from the 624 cerebral venous thrombosis patients in ISCVT[11].

VITT patients were significantly younger (median age in years 47, IQR 23) than non-VITT patients (median 57, IQR 21, p=0.0045). All 70 cases of VITT-associated cerebral venous thrombosis occurred after a first dose of the ChAdOx1 (AstraZeneca) vaccine, compared with 21/25 (84%) of patients with non-VITT cerebral venous thrombosis (p=0.0040); the other 4 patients had been given their first dose (3 patients) or second dose (1 patient) of BNT162b2 (Pfizer) vaccine. The clinical features of cerebral venous thrombosis were similar in the VITT and non-VITT groups (Table S3).

Patients with VITT-associated cerebral venous thrombosis had a lower admission fibrinogen (2.0 g/L, IQR 1.5 g/L) than the non-VITT group (3.3 g/L, IQR 1.2 g/L) although both medians were within the normal range (1.9-4.3 g/L). Table 1 and Figure S4). Of the 58 patients with VITT who were investigated for anti-PF4 antibodies using an ELISA assay, 56 (97%) tested positive; the characteristics of the other two patients are given in the Supplementary Materials (Patients E and F in Table S2). Two patients with anti-PF4 antibodies on ELISA were classified as non-VITT using the current criteria, one because her platelet count never fell below 150 $x10^9$/L (Patient B, Table S2, Supplementary Materials) and the other because her D-dimers never rose above 2000 mg/L (Patient C, Table S2, Supplementary Materials).

Pattern of venous thrombosis and brain parenchymal involvement

The number of veins thrombosed on the first venogram performed was higher in our VITT group (median 3, IQR 2) than in our non-VITT group (median 2, IQR 1, p=0.041, Table S4 and Figure S5). On neuroimaging done at the time of admission, patients with VITT were more likely to have evidence of multiple venous infarction (10/70, 14%) than those without VITT (0/25, 0.046) and more likely to have multiple intracerebral haemorrhages (23/70, 33%) than non-VITT patients (3/25, 12%, p=0.045, Supplementary Materials, Table S4).

31 of the 70 patients with VITT-associated cerebral venous thrombosis (44%) had evidence of extracranial venous thrombosis, arterial thrombosis, or both, with pulmonary embolism and hepatic portal vein thrombosis being particularly common (Table S4). By contrast, extracranial thrombosis was only seen in one out of the 25 patients classified as non-VITT (4%). This woman (Patient D, Table S2,

Supplementary Materials) had pulmonary embolism and hepatic vein thrombosis in addition to cerebral venous sinus thrombosis and presented with a platelet count of 57 x10^9/L. Even though she was not classified as having VITT in this study, because her highest D-dimer was only 822 μg/L, the clinical team treated her for VITT.

Outcome at the end of admission

Figure 3 shows the modified Rankin scale (mRS)[12] on discharge for VITT patients compared with the non-VITT group (Figure 3A) or with the ISCVT cohort (Figure 3B). The primary outcome, death during admission or dependency on others at the time of discharge (mRS 3-6), was significantly more common in VITT-associated cerebral venous thrombosis (33/70, 47%) than in non-VITT patients (4/25, 16%, p=0.0061). More patients died during admission in the VITT-associated cerebral venous thrombosis group (20/70, 29%) than in the non-VITT group (1/25, 4%, p=0.011). Low Glasgow Coma Scale (GCS[14]) on admission and cerebral haemorrhage were the strongest predictors of death or dependency (Table S5), as expected in cerebral venous thrombosis[11].

Table 2 shows how many VITT patients were offered each type of treatment and, of these, the proportion that were dead or dependent (mRS 3-6) at the end of their admission. Among patients treated with parenteral anticoagulants, 52 were given just one out of the two options of heparin (low molecular weight or unfractionated) or a non-heparin parenteral alternative (argatroban or fondaparinux). This choice appears to have been determined mainly by the treatment date rather than patient characteristics: among patients with VITT, up to 12th March 2021 heparins were used, between 13th March and 18th March 2021 there was a mixture, and from 19th March onwards only non-heparin intravenous agents were used (except for one patient who was given unfractionated heparin briefly before switching to argatroban later that day). Of the nine patients with VITT-associated cerebral venous thrombosis who received some form of heparin as their only parenteral anticoagulant, six were dead or dependent at the end of their admission (67%), whereas among the 43 patients given a non-heparin alternative as their only parenteral anticoagulant, only 16 had this poor outcome (37%), although this difference was not significant (p=0.14).

Among patients with VITT-associated cerebral venous thrombosis, the proportion of patients who were dead or dependent at the end of their admission was lower in the group treated with intravenous immunoglobulin (22/55, 40%) than in those who were not given this treatment (11/15, 73%, p=0.022).

Discussion

Our data provide the most detailed information on the clinical and radiological characteristics of VITT-associated cerebral venous thrombosis reported to date. The age distribution of our whole patient population was skewed towards older age groups because of the UK policy of vaccinating older patients first, but patients with VITT-associated cerebral venous thrombosis were younger than those without VITT. Other key findings were that, compared with non-VITT patients, those with VITT-associated cerebral venous thrombosis had more extensive venous thrombosis and higher rates of multiple infarcts, multiple intracerebral haemorrhages and extracranial thrombosis. VITT was associated with significantly more death or dependency at the end of admission, but both the use of non-heparin anticoagulants and of intravenous immunoglobulin were associated with an improved outcome. As these treatments become better established, the outcome from VITT-associated cerebral venous thrombosis may improve over time.

The ratio of VITT to non-VITT patients was 2.8:1, as expected from the estimated incidence of VITT-associated cerebral venous thrombosis in individuals receiving a first dose of the ChAdOx2 vaccine (12.3 per million[15]) and the expected background incidence of cerebral venous thrombosis in the same sub-population during the four month study period (4.4 per million[16]), suggesting that cerebral venous thrombosis was probably unrelated to vaccination in most or all of our non-VITT cases and that there was no significant bias towards reporting VITT cases.

A "normal" platelet count (conventionally ≥ 150 x10^9/L) is regarded as ruling out VITT in existing peer-reviewed published guidelines[17,18] but adopting a platelet count threshold of <150 x10^9/L as a criterion for VITT-associated cerebral venous thrombosis in the present study may have been a weakness. Firstly, defining thrombocytopenia as a fall to less than 50% of a known baseline platelet count is recommended in the analogous condition of HIT[19]. Secondly, Patient B (Supplementary Materials, Table S2), who was excluded from our VITT group because her platelet count never dipped below 150 x10^9/L, was treated as having VITT because of her positive anti-PF4 antibodies and very high D-dimer of 4,985 μg/L. Although we regard thrombocytopenia as the hallmark for VITT, adopting a hard threshold of 150 x10^9/L for defining thrombocytopenia risks excluding patients who have good evidence for VITT.

In addition, making D-dimer > 2000 μg/L an absolute requirement for diagnosis of VITT-associated cerebral venous thrombosis may have been suboptimal. Patient C (Table S2, Supplementary Materials) had cerebral venous thrombosis, a platelet count of 110 x 10^9/L and positive anti-PF4 antibodies, strong evidence for VITT, but even after repeated testing her D-dimer was never higher than 410 μg/L.

Patient D (Table S2, Supplementary Materials) had a lowest platelet count of 37 x 10^9/L and in addition to her cerebral venous thrombosis had evidence of hepatic vein thrombosis, suspicious for VITT even though her anti-PF4 antibody was negative, yet her highest D-dimer was only 822 μg/L. Neither met the current criteria for VITT-associated cerebral venous thrombosis used in this study, yet both were judged to have VITT by their treating clinicians.

Aside from the lowest platelet count and highest D-dimer that were used to make the diagnosis of VITT-associated cerebral venous thrombosis, three other features showed a highly significant association ($p<0.001$) with the diagnosis: anti-PF4 antibodies, fibrinogen and extracranial venous thromboses. The specificity of anti-PF4 antibodies was probably underestimated in our study, as the only two patients who were positive for the antibody but were classified as non-VITT using current criteria were Patients B and C (Table S2, Supplementary Materials), i.e. patients with probable VITT who were most likely mis-classified. On the other hand, Patients E and F (Table S2, Supplementary Materials) had strong evidence for VITT but both were negative for anti-PF4 antibodies on two different ELISA assays, suggesting that a negative ELISA result should not be used to define VITT as "unlikely"[18] or to cease further investigation[17], as is recommended in existing guidelines[17,18].

These observations lead us to propose the new set of diagnostic criteria for VITT-associated cerebral venous thrombosis given in the Panel. A diagnosis of Possible VITT-associated cerebral venous thrombosis will alert clinicians to the urgent need for further investigation for this condition and they are likely to avoid the use of heparins or platelet transfusions if possible. A diagnosis of Probable VITT constitutes sufficient evidence to offer a patient full treatment for this condition, including intravenous immunoglobulin or plasma exchange. A Definite diagnosis will be useful for defining a population for future research studies into this condition. According to these criteria it is possible to make a diagnosis of Probable VITT even in patients with a normal platelet count (≥ 150 x109/L), a normal D-dimer or a negative anti-PF4 antibody test, provided other evidence strongly supports the diagnosis.

In patients with cerebral venous thrombosis following COVID-19 vaccination, anti-PF4 testing should not be reserved for patients with admission platelet counts below 150 x10^9/L. This strategy would risk missing patients with VITT. A patient with a low-normal platelet count may still have anti-PF4 antibodies, as was the case for Patient B (Table S2, Supplementary Materials), and a diagnosis of VITT should still be considered whilst further diagnostic tests are undertaken, including further full blood counts.

Clinicians should be aware that patients with VITT-associated cerebral venous thrombosis are more likely to have extracranial thrombosis than other patients with cerebral venous thrombosis. Some patients, such as Patient A (Figure 1), may be dysphasic and have difficulty reporting their symptoms.

Anticoagulation and treatment with intravenous immoglobulin were associated with a lower probability of death or dependency at the end of hospital admission, but this observation is difficult to interpret as the most unwell patients may have died before these treatments could be offered, biasing the results. Similarly the association between decompressive hemicraniectomy and poor outcome probably reflects selection of patients with the most severe cerebral venous thrombosis for this invasive procedure. All the same, the mortality rate of 54% after decompressive hemicraniectomy for VITT-associated cerebral venous thrombosis is high compared with a historical mortality of 16% after this procedure in cerebral venous thrombosis[20].

The relationship between platelet transfusion and poor outcome in VITT-associated cerebral venous thrombosis appears to confirm concerns about the safety of this treatment[3], but the result is again difficult to interpret, because in 12/25 (48%) of patients offered this treatment, the indication was to support decompressive hemicraniectomy, which was only offered to patients with severe cerebral venous thrombosis.

Strengths of our study are that we present the largest and most detailed study of VITT-associated cerebral venous thrombosis with a well-matched control group consisting of patient presenting to UK hospitals with cerebral venous thrombosis following vaccination against COVID-19 but without evidence of VITT. Limitations are that the number of patients in each group in our study was small, because of the rarity of these conditions. The study was underpowered for some of the comparisons made between the VITT and non-VITT groups. Although our study will generate important hypotheses for future study, we cannot draw inferences about other populations of patients with cerebral venous thrombosis following COVID-19 vaccination. On the other hand comparison of our patients with the much larger historical ISCVT cohort[11] may have been confounded by the higher age of our patients, attributable to COVID-19 vaccination policy in the UK rather than to VITT. The median interval between vaccination and symptom onset may be an underestimate; in some cases in which the first symptom of cerebral venous thrombosis was reported as headache, this symptom may initially have been caused by mechanisms other than cerebral venous thrombosis, and also patients with a shorter interval may have been preferentially reported. We were dependent on local radiology reports for interpretation of scans, and on routine clinical observations, laboratory tests and radiology which may have led to indication bias. For example, we found only one patient with anti-PF4 antibodies but normal platelets (Patient B, Table S2, Supplementary Materials), but 9/20 of the patients with normal

platelets were not checked for anti-PF4 antibodies, so other cases with this combination may have been missed. We were unable to draw firm conclusions about treatments for VITT-associated cerebral venous thrombosis because we could not control for differences in the baseline characteristics between patients offered or not offered those treatments.

In conclusion, we have described the clinical features of VITT-associated cerebral venous thrombosis in detail, allowing us to propose diagnostic criteria for this condition. We recommend that all patients presenting with cerebral venous thrombosis within 28 days of COVID-19 vaccination should be checked for anti-PF4 antibodies, whatever the platelet count, until there are sufficient data to set an upper limit on the platelet count with which VITT-associated cerebral venous thrombosis may occur. We have shown that VITT-associated cerebral venous thrombosis has a worse outcome than other forms of cerebral venous thrombosis and our data suggest that non-heparin anticoagulants and immunoglobulin may improve outcome of VITT-associated cerebral venous thrombosis. However, VITT appears to be a very rare side-effect of vaccination with the ChAdOx1 vaccine, the risk of which is likely to be greatly outweighed by the benefit of vaccination against COVID-19 for most people[21].

	VITT (V)	Non-VITT (N)	P (V vs N)	ISCVT (I)	P (V vs I)
Age and sex	n=70	n=25		n=624	
Age median (IQR)	47 (23)	57 (21)	0.0045	37	0.0001
Female (%)	39/70 (56)	11/25 (44)	0.31	465/624 (75)	0.001
Ethnicity	n=70	n=25		n=621	
White (%)	61/70 (87)	21/25 (84)	0.74	550/621 (89)	0.72
Asian (%)	7/70 (10)	2/25 (8)	1.0	21/621 (3)	0.017
Black (%)	0/70 (0)	1/25 (4)	0.26	31/621 (5)	0.063
Other / mixed (%)	2/70 (3)	1/25 (4)	1.0	19/621 (3)	1.0
Vaccine details	n=70	n=25			
Proportion given AstraZeneca (%)	70/70 (100)	21/25 (84)	0.0040		
Median days from vaccine to cerebral venous thrombosis (IQR)	9 (5)	11 (15)	0.10		
Venous risk factors (RF)	n=70	n=25			
Patients with no venous RFs	46/70 (66)	11/25 (44)	0.057	Not given	
Patients with no ISCVT RFs	61/70 (87)	20/25 (80)	0.51	78/624 (13)	<0.0001
Fibrinogen	n=59	n=15			
Median in g/L (IQR)	2.0 (1.5)	3.3 (1.2)	0.0001		
Prothrombin time	n=69	n=24			
Median in seconds (IQR)	13.0 (2.9)	11.5 (1.8)	0.0005		
Activated partial thromboplastin time	n=67	n=24			
Median in seconds (IQR)	28.8 (9.7)	26.9 (8.3.0)	0.030		
Anti-PF4 antibodies					
Positive on ELISA (%)	56/58 (97)	2/16 (13)	<0.0001		
Positive on Acustar HIT-IgG assay (%)	3/13 (23)	0/5 (0)	0.52		

Data compared between VITT-associated cerebral venous thrombosis patients and the non-VITT cerebral venous thrombosis patients in the present study (V vs N) and between the VITT-associated cerebral venous thrombosis patients and the historical cerebral venous thrombosis data set from the ISCVT[11] (V vs I). Categorical variables were compared using chi squared test; continuous variables were compared using Mann-Whitney U test. Blood results were the closest available to the admission date. Normal ranges are typically fibrinogen 1.9-4.3 g/L, prothrombin time 10-13 seconds, activated partial thromboplastin time 23-30 seconds.

Table 1: **Comparison of the demographics, vaccine details and blood results on admission between patients with VITT-associated cerebral venous thrombosis and those with non-VITT cerebral venous thrombosis (from this study and from ISCVT)**

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		No. of patients treated / not treated	No. of patients dead or dependent (%)	P value
Pharmacological				
Any anticoagulation	Yes	60	24 (40)	0.0047
	No	10	9 (90)	
Heparin/LMWH	Yes	16	8 (50)	1.0
	No	54	25 (46)	
Non-heparin parenteral anticoagulant	Yes	50	18 (36)	0.0031
	No	20	15 (75)	
DOAC	Yes	22	4 (18.2)	0.0016
	No	48	29 (60)	
Corticosteroid	Yes	51	22 (43)	0.27
	No	19	11 (58)	
Anticonvulsant	Yes	26	13 (50)	0.71
	No	44	24 (55)	
Fibrinogen replacement	Yes	15	7 (47)	1.00
	No	55	26 (47)	
IV immunoglobulin	Yes	55	22 (40)	0.022
	No	15	11 (73)	
Plasma exchange	Yes	16	7 (44)	0.78
	No	54	26 (48)	
Platelet transfusion	Yes	25	21 (84)	<0.0001
	No	45	12 (27)	
Invasive				
Endovascular management	Yes	9	5 (56)	0.73
	No	61	28 (46)	
Intracranial pressure monitor	Yes	13	13 (100)	<0.0001
	No	57	20 (35)	
Decompressive hemicraniectomy	Yes	13	13 (100)	<0.0001
	No	57	20 (35)	

P values are for chi squared tests comparing the proportion of patients left dead or dependent (mRS 3-6) at the end of their admission, in patients treated compared with those not treated.

Table 2: **Proportions of patients with VITT-associated cerebral venous thrombosis who were dead or dependent at the end of their admission, by treatment modality**

Panel: **Diagnostic criteria for VITT-associated cerebral venous thrombosis**

Definite VITT-associated cerebral venous thrombosis	**Post-vaccine cerebral venous thrombosis** (proven on neuroimaging and with first symptom of venous thrombosis within 28 days of vaccination against COVID-19 vaccination) *and* **Thrombocytopenia** (lowest recorded platelet count < 150 x10^9/L or documented platelet count decrease to less than 50% of baseline) *and* **Anti-PF4 antibodies** (on ELISA assay or functional assay)
Probable VITT-associated cerebral venous thrombosis	**Post-vaccine cerebral venous thrombosis** *and* Either **thrombocytopenia** or **anti-PF4 antibodies** on ELISA assay *and* **Coagulopathy** (D-dimer > 2000 μg/L or fibrinogen < 2.0 g/L with no other explanation (such as severe sepsis, malignancy, recent trauma or surgery) or **Extracranial venous thrombosis** (clinical or imaging evidence of with onset since COVID-19 vaccination)
Possible VITT-associated cerebral venous thrombosis	**Post-vaccine cerebral venous thrombosis** *and* Either **thrombocytopenia** or **anti-PF4 antibodies**

In assessing the interval since vaccination, the date of the first symptom of venous thrombosis should be used, even if this was a symptom of an extracranial thrombosis. The retrospective time window within which a pre-cerebral venous thrombosis baseline platelet count may be used to define a fall of greater than 50% has not been defined as it will depend on what medical events have occurred in the interim.

Contributors

CR and RJP conceived the study. The Steering Committee comprised RJP, AW, TS, MS, DJW and CR. RJP wrote the protocol and clarified the regulatory framework of the study. TS, AT and BS independently initiated a similar study that was amalgamated into this one. RJP designed the Case Report Form and AT, BS, PF, AW, MS, DJW and CR provided critical review of its content. RJP designed, implemented and maintained the database and uploaded the data. RJP, AT and BS continuously reviewed the data to ensure its validity and submitted data queries where there were errors or omissions. BC provided data on where cases had been seen. RJP, AT, RM, PA-F, JMY, LZ, MJ, EH, DWh, PF, AW coordinated data collection in their sites and submitted case report forms. GH-S, CH, DWa submitted case report forms. RJP performed statistical analysis and wrote the manuscript. All authors critically reviewed the manuscript.

Disclosures

RP receives grants from Randox Laboratories Ltd on an unrelated subject and from The Stroke Association for work on COVID-19 and stroke, not related to vaccination. PA-F receives grants from the Wellcome Trust for work on an unrelated subject. EH receives grants from MND Scotland and the NIHR for work on an unrelated subject. TS sits on the MHRA Vaccine Benefit Versus Risk Expert Working Group and was on the Data Safety Monitoring Committee of the GSK Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children GSK3390107A (ChAd3 EBO-Z) vaccine. He is supported for COVID-19 work by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (Grant No. NIHR200907), NIHR Global Health Research Group on Brain Infections (No. 17/63/110), the UK Medical Research Council's Global Effort on COVID-19 Programme (MR/V033441/1). MS receives grants from Shire, Novartis and has received personal fees from Takeda, Novartis, Octapharma and Sanofi for work on unrelated subjects. BS receives a grant from the MRC, via the UKRI/NIHR Global Effort on COVID-19 Research (GECO) to study neurological disease in relation to COVID-19 and he has been a case management consultant to WHO-SEARO via GOARN since April 2020, but vaccination against the infection is not the focus of this work in either case. CR receives grants from the NIHR for work on an unrelated subject and is also collaborating with FirstKind Medical on a grant on an unrelated subject. She is Chair of the NIHR Hyperacute Stroke Research Oversight Group and is a member of the European Stroke Organization board of Directors. DJW has received personal fees from Bayer, Alnylam and Portola, not related to the work presented here. The other authors have no disclosures.

Approvals

CAIAC is a surveillance study. The Sponsor (Joint Research Office, University College London,UK) and the Health Research Authority, UK confirmed this status and that collection of anonymised routine data could proceed without patient consent.

Data sharing

After publication, anonymised individual patient data will be made available on any reasonable request made to the Corresponding Author, subject to a Data Sharing Agreement and the constraints imposed by UK data control and research governance regulations.

Acknowledgements

The authors would like to thank the wider group of CAIAC collaborators, listed in the Supplementary Materials, who submitted cases. Thanks also to the British Association of Stroke Physicians and the Association of British Neurologists for promoting the study. This work was undertaken at UCL Hospitals/UCL, which receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centre's funding scheme. RP is supported by The Stroke Association for his work on COVID-19 and stroke. TS is supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (Grant No. NIHR200907), NIHR Global Health Research Group on Brain Infections (No. 17/63/110), the UK Medical Research Council's Global Effort on COVID-19 Programme (MR/V033441/1) for his work on Covid-19 and neurological disease including stroke. TS and BS are supported by the NIHR Global Health Research Group on Brain Infections (No. 17/63/110).

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Cerebral venous sinus thrombosis following vaccination against COVID-19: a UK multicentre cohort study

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Figures

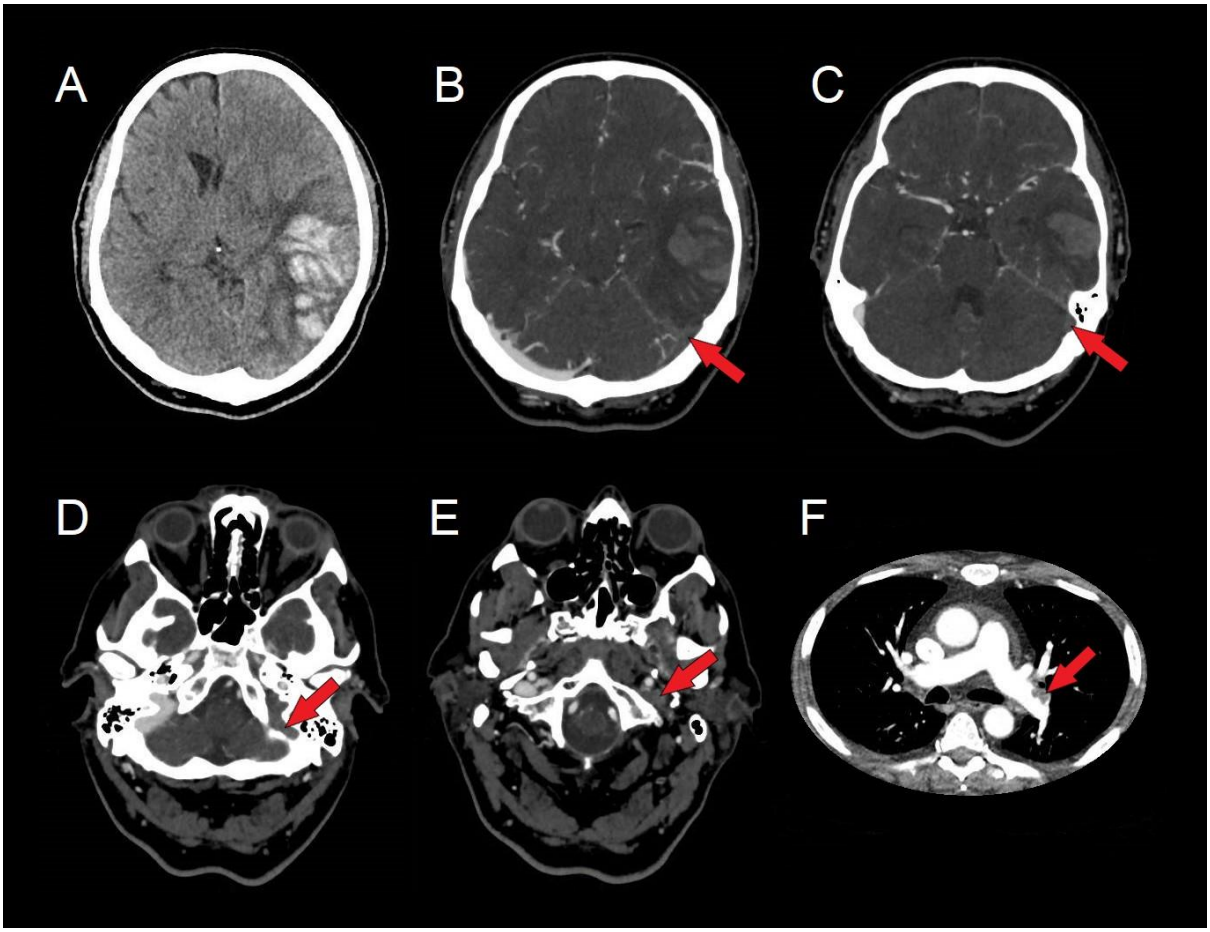

Figure 1: Imaging for Patient A, with typical VITT-associated CVST

This man in his 50s was well prior to vaccination with the ChAdOx1 vaccine, but 17 days later developed a headache, abdominal pain, vomiting, dysphasia and confusion. A. Axial CT without contrast showing a large haemorrhagic venous infarct in the left temporal lobe. B-E. Axial CT venogram. Arrows indicate voids left by thrombus in the left transverse sinus (B,C) and the left sigmoid sinus (D) and lack of opacification of the left internal jugular vein (E). Each structure can be compared with its well-opacified counterpart on the right side. F. CT pulmonary angiogram showing thrombus in the left pulmonary artery. The patient's details are given in the Supplementary Materials (Table S2, Patient A).

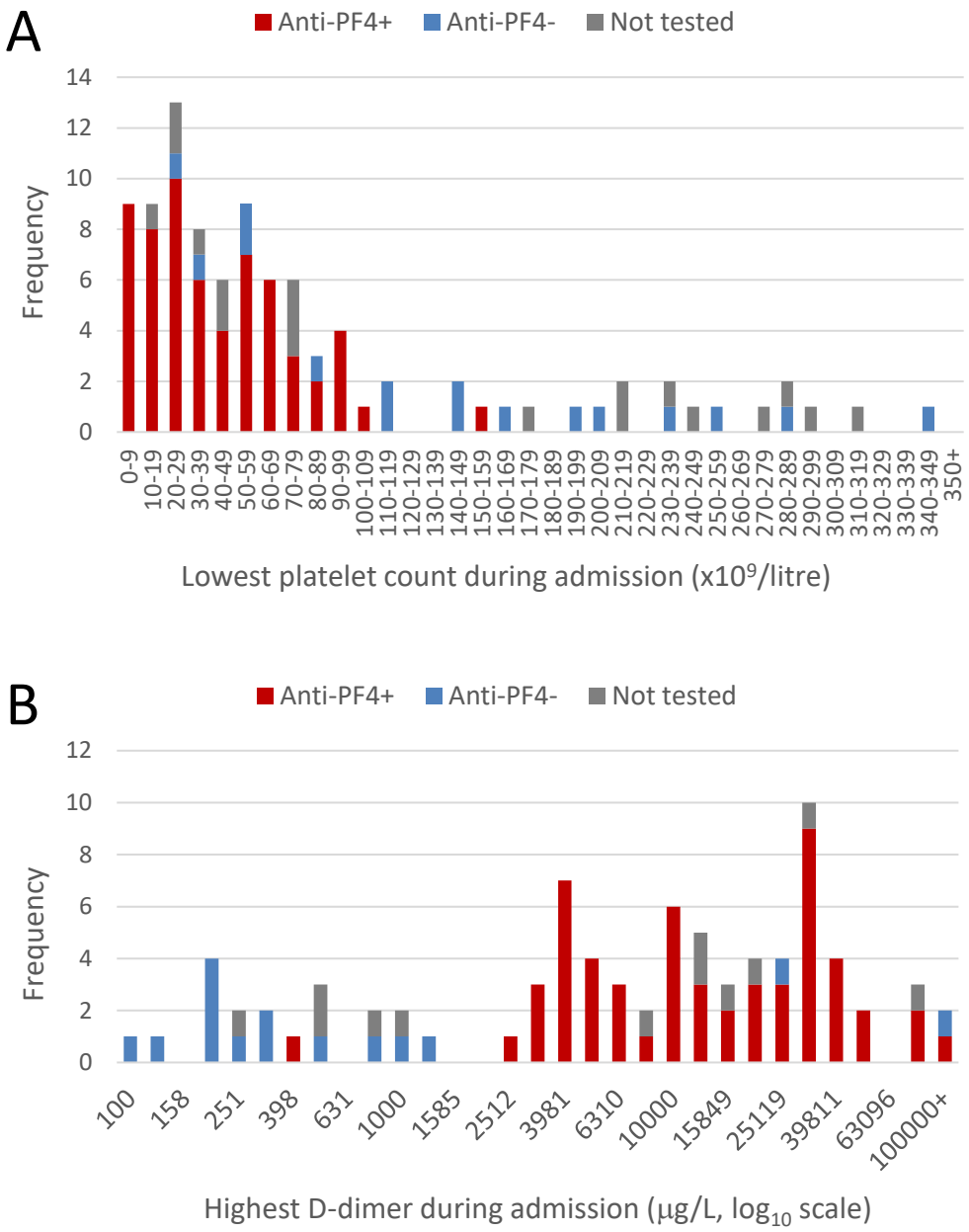

Figure 2: Distributions of lowest platelet counts (A) and highest D-dimers (B) recorded during admission, in patients with anti-PF4 antibodies (red), without PF4 antibodies (blue) or not tested (grey)

76/95 patients (80%) were tested for anti-PF4 antibodies either by ELISA or a functional assay or both. Patients were counted as anti-PF4+ if the result by either method was positive; this group includes 18 patients in whom the ELISA test was positive but the functional assay was negative. The x axis labels represent the lowest limit of the bin. Patients with atypical anti-PF4 results are described in Table S2 (Supplementary Materials) as follows: the patient with a normal platelet count and positive anti-PF4 antibodies is Patient B; the patient with normal D-dimers and positive anti-PF4 antibodies is Patient C; the two patients with high D-dimers and negative anti-PF4 antibodies are Patients E and F. The value of $\log_{10}$(D-dimer in μg/L) lying between the two empty bars (the lower one of which is labelled as "1585") was 3.3, equivalent to D-dimers = 1995 μg/L.

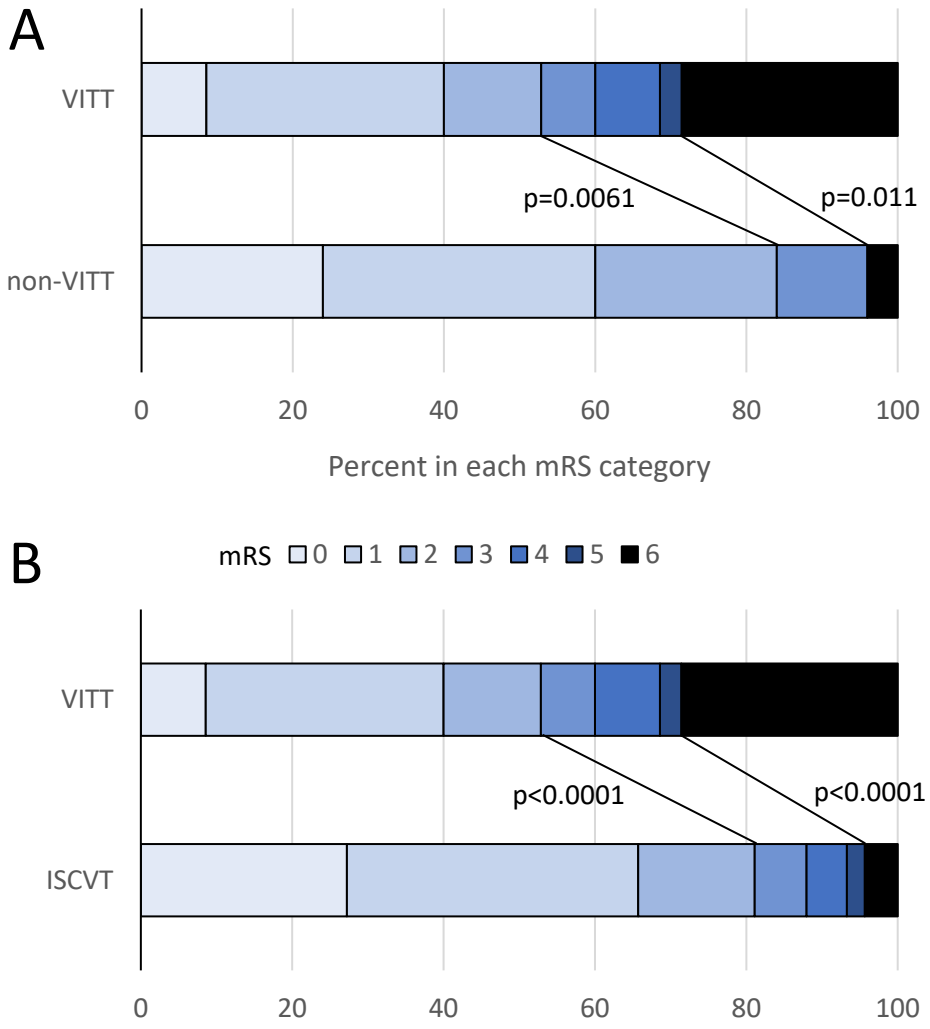

Figure 3: Disability on discharge

A. Comparison between VITT and non-VITT patients with CVST. B. Comparison between VITT-associated CVST and historical data from ISCVT[11]. Each horizontal bar represents the percentage of patients in each modified Rankin scale category[12], which varies from zero (no symptoms) through to 5 (severe disability). 6 represents death during this admission. Diagonal lines and p values are for comparisons for death and dependency (mRS = 3-6) or for death (mRS = 6).

Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study

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Appendix

List of CAIAC collaborators

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Venous risk factors recorded

Venous risk factors listed in the ISCVT[12] were designated 'ISCVT risk factors' and analysed separately so that a direct comparison with ISCVT could be made. These were: combined oral contraceptive pill or HRT; pregnancy or recent childbirth; thyroid disease; dehydration; malignancy or myeloproliferative disorder; recent neurosurgery; head injury or lumbar puncture; Behçet syndrome or SLE; antiphospholipid syndrome or other acquired thrombophilia; inherited thrombophilias; intracranial infection and inflammatory bowel disease.

However we also present data on a broader collection of known or putative venous risk factors, which in addition to the factors above included: obesity; smoking; chronic renal disease; previous DVT or PE and family history of venous thrombo-embolism.

Staged roll-out of vaccination by age criteria in the UK during 2021

At the time of this study, most vaccination in the UK was offered according to age criteria, starting with people aged 80 and over, and then progressively working downwards through the other age groups. Up to 12th April 2021 all individuals aged 50 and over were offered vaccination and from 13th April individuals aged 45 and over were offered vaccination. The vaccine was only routinely offered to patients aged 40-45 years after 30th April, which was the last date of vaccination of any of the individuals included in the present study. A minority of individuals were vaccinated using criteria other than age, such as those with a very high risk from COVID-19 and their carers, frontline health or social care workers, individuals who lived or worked in care homes and individuals with learning difficulties.

Appendix tables

		ELISA			
		Positive	Negative	Not tested	Total
Acustar HIT-IgG assay	Positive	3	0	0	3
	Negative	9	5	0	14
	Not tested	46	11	21	78
	Total	**58**	**16**	**21**	**95**

ELISA assays were Stago Asserachrom, Immucor Lifecodes or Hyphen Zymutest.

Table A1: **Contingency table of testing for anti-PF4 antibodies using ELISA or a functional assay, all study patients included**

Patient	A	B	C	D	E	F
Sex	Male	Female	Female	Female	Female	Female
Age group (decade)	50s	50s	50s	60s	50s	50s
Vaccine given	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1	ChAdOx1
Interval (days)	17	14	20	8	8	8
Symptoms	Headache, abdominal pain, vomiting, dysphasia	Headache, dysphasia	Headache	Headache, dysphasia, drowsiness	Headache	Headache, left facial weakness, left neglect
Admission platelet count ($x10^9$/L) NR 150-400	73	158	110	57	37	57
Lowest platelet count ($x10^9$/L) NR 150-400	73	158	110	34	24	57
Highest platelet count after treatment ($x10^9$/L) NR 150-400	259	355	223	(768*)	106	374
Admission D-dimer (μg/L) NR 220-460	6,177	4,985	370	822	119,913	29,503
Highest D-dimer (μg/L) NR 220-460	22,730	4,985	410	822	119,913	29,503
Fibrinogen (g/L) NR 1.9-4.3	2.9	2.0	2.8	2.1	0.83	2.0
Anti-PF4 IgG antibody Stago Asserachrom ELISA (OD) NR 0 - 0.238	0.827 (+ve)	0.594 (+ve)	Not done	Not done	0.177 (-ve)	0.078 (-ve)
Anti-PF4 IgG antibody Immucor Lifecodes ELISA (OD) NR 0 - 0.400	Not done	1.41 (+ve)	2.20 (+ve)	0.298 (-ve)	Not done	Not done
Anti-PF4 IgG antibody Hyphen Zymutest ELISA (OD) NR 0 - 0.239	Not done	Not done	Not done	Not done	0.082 (-ve)	0.035 (-ve)
Brain parenchyma	Haemorrhagic infarct in left temporal lobe	Left ICH	Normal	Right focal oedema	Normal	Right focal oedema. ICH
Intracranial sinuses or veins thrombosed	Left TS, SS, IJV	Left TS, SS	Right TS, SS.	Right TS, SS	Left CVT. Left SOV, IOV	Right TS, SS, IJV
Extracranial thrombosis	Left PA. HVs, HPV, SV, SMV	None	None	HVs	None	None
Parenteral anticoagulant	SC fondaparinux	None	SC fondaparinux	SC enoxaparin	SC fondaparinux	IV argatroban
Oral anticoagulant	Apixaban	Apixaban	Warfarin	Warfarin	Dabigatran	Apixaban
Oral steroids	None	Prednisolone	Prednisolone	Prednisolone	Prednisolone	None
Plasma exchange	Yes	No	No	No	No	No
IV immunoglobulin	Yes	No	Yes	No	Yes	Yes
mRS on discharge	3	2	0	2	2	1
VITT on Starting Criteria	Yes	No	No	No	Yes	Yes

*Platelet count after platelet transfusion. Precise ages are not given to protect the identities of the patients. ChAdOx1 first dose of ChAdOx1 (AstraZeneca) vaccine. NR normal range, OD optical density, ICH intracerebral haemorrhage, TS transverse sinus, SS sigmoid sinus, IJV internal jugular vein, CVT cortical vein thrombosis, SOV superior ophthalmic vein, IOV inferior ophthalmic vein, HVs hepatic veins, HPV hepatic portal vein, SV splenic vein, SMV superior mesenteric vein, PA pulmonary artery.

Table A2: **Characteristics of index patients referred to in the text**

	VITT	Non-VITT	p value (VITT vs non-VITT	ISCVT	p value (VITT vs ISCVT)
Headaches	59/70 (84%)	21/25 (84%)	1.0	553/623 (89%)	0.27
Limb weakness	34/70 (49%)	9/25 (36%)	0.28	232/624 (37%)	0.063
Nausea / vomiting	31/70 (44%)	6/25 (24%)	0.074	Not given	
Drowsiness	23/70 (33%)	4/25 (16%)	0.11	Not given	
Confusion	19/70 (27%)	7/25 (28%)	0.93	137/624 (22%)	0.32
Seizures	20/70 (29%)	5/25 (20%)	0.40	245/624 (39%)	0.081
Visual field defect	13/70 (19%)	4/25 (16%)	1.0	Not given	
Language disturbance	12/70 (17%)	7/25 (28%)	0.26	119/624 (19%)	0.70
Facial weakness	10/70 (14%)	0/25 (0%)	0.06	Not given	
Limb sensory disturbance	10/70 (14%)	4/25 (16%)	1.0	Not given	
Other cortical	10/70 (14%)	0/25 (0%)	1.0	Not given	
Blurred vision	10/70 (14%)	4/25 (16%)	1.0	Not given	
Limb clumsiness / ataxia	9/70 (13%)	3/25 (12%)	1.0	Not given	
Papilloedema	7/70 (10%)	1/25 (4%)	0.35	174/614 (28%)	0.0010
Diplopia or IIIrd or VIth nerve palsy	3/70 (4%)	1/25 (4%)	1.0	84/624 (13%)	0.028
Other cranial neuropathy	2/70 (3%)	0/25 (0%)	1.0	Not given	
Vertigo	1/70 (1%)	1/25 (4%)	0.46	Not given	

Data compared between VITT-associated CVST and the historical CVST data set from the ISCVT (V vs I)[10] and between the VITT-associated and non-VITT-associated CVST patients in the present study (V vs N). Variables were compared using the chi squared test.

Table A3: **Clinical features of CVST at the time of admission in patients with and without VITT**

	VITT	Non-VITT	p value (VITT vs non-VITT)	ISCVT (I)	p value (VITT vs ISCVT)
Sinuses / veins occluded					
Superior sagittal sinus	43/70 (61%)	12/25 (48%)	0.24	313/624 (50%)	0.074
Left transverse sinus	33/70 (47%)	11/25 (44%)	0.79	279/624 (45%)	0.70
Right transverse sinus	31/70 (44%)	9/25 (36%)	0.47	257/624 (41%)	0.62
Left sigmoid sinus	25/70 (36%)	9/25 (36%)	0.98	Not given	
Right sigmoid sinus	25/70 (36%)	7/25 (28%)	0.48	Not given	
Cortical veins	14/70 (20%)	7/25 (28%)	0.41	107/623 (17%)	0.55
Deep venous system	10/70 (14%)	1/25 (4%)	0.28	68/622 (11%)	0.40
Straight sinus	11/70 (16%)	1/25 (4%)	0.17	112/623 (18%)	0.64
Inferior sagittal sinus	5/70 (7%)	2/25 (8%)	1.0	Not given	
Cavernous sinus	3/70 (4%)	0/25 (0%)	0.56	8/623 (1%)	0.057
Internal jugular veins	26/70 (37%)	8/25 (32%)	0.65	74/624 (12%)	<0.0001
Median number of sinuses or veins thrombosed (IQR)	3 (2-4)	2 (2-3)	0.041	Not given	
Brain parenchyma involvement					
Any infarct or haemorrhage	44/70 (63%)	14/25 (56%)	0.55	392/624 (63%)	1.0
Any infarcts	14/70 (20%)	4/25 (16%)	0.66	290/623 (47%)	<0.0001
Multiple infarcts	10/70 (14%)	0/25 (0%)	0.046	Not given	
Any haemorrhages	41/70 (59%)	10/25 (40%)	0.11	245/622 (39%)	0.0020
Multiple haemorrhages	23/70 (33%)	3/25 (12%)	0.045	Not given	
Extracranial thromboses					
Any extracranial thrombosis	31/70 (44%)	1/25 (4%)	0.0003		
Pulmonary embolism	14/70 (20%)	1/25 (4%)	0.11		
Hepatic portal vein thrombosis	13/70 (19%)	0/25 (0%)	0.018		
Deep vein thrombosis in le	6/70 (9%)	0/25 (0%)	0.34		
Arterial limb ischaemia	4/70 (6%)	0/25 (0%)	0.57		
Superior mesenteric vein thrombosis	4/70 (6%)	0/25 (0%)	0.57		
Myocardial infarction	2/70 (3%)	0/25 (0%)	1.0		
Splenic vein thrombosis	2/70 (3%)	0/25 (0%)	1.0		
Hepatic vein thrombosis	1/70 (1%)	1/25 (4%)	0.46		
Arterial ischaemic stroke	2/70 (3%)	0/25 (0%)	0.34		

Data compared between the VITT-associated CVST and non-VITT CVST in the present study (V vs N) and between VITT-associated CVST and the historical CVST data set from the ISCVT (V vs I)[11]. Categorical variables were compared using chi squared test (or Fisher's exact test if fewer than 5 patients in any one category); continuous variables were compared using Mann-Whitney U test.

Table A4: **Sites of thrombosis and brain parenchyma involvement in VITT and non-VITT groups**

	Dead or dependent	Alive and independent	p value
Number of VITT cases	33	37	
Demographics			
Median age (IQR)	52 (34-58)	46 (30-51)	0.12
Female	19 (58%)	20/37 (54%)	0.77
Male	14 (42%)	17/37 (46%)	
Clinical assessment			
History of malignancy	2 (6%)	0 (0%)	0.22
Median admission GCS (IQR)	14 (12-15)	15 (15-15)	<0.0001
Blood biomarkers			
Median platelets (IQR)	34 (22-67)	50 (34-80)	0.078
Median D-dimers (IQR)*	12895 (8826-36125)	16280 (5096-29692)	0.17
Median fibrinogen (IQR)	1.8 (1.0-2.7)	1.7 (1.0-2.5)	0.45
Anti-PF4 antibody positive	26/26 (100%)	32/34 (94%)	0.21
Neuroradiological biomarkers			
Cerebral infarction	7 (21%)	7 (19%)	1.0
Any cerebral haemorrhage	27 (82%)	14 (38%)	0.0002
Multiple cerebral haemorrhages	17 (52%)	6 (16%)	0.0017
Median veins thrombosed (IQR)	3 (3-4)	3 (2-4)	0.19
Thrombosis of deep veins	5 (15%)	5 (14%)	1.0

Results are those which were obtained on admission or as close as possible to admission. For categorical variables, the proportion of patients with the characteristic is shown, followed by the percentage in parenthesis. For continuous variables, the median is shown with the interquartile range (IQR) in parenthesis. *D-dimer result available in 27/33 dead or dependent patients and 35/37 alive and independent patients.

Table A5: **Admission characteristics in patients with VITT-associated CVST according to whether or not they were dead or dependent (mRS 3-6) at the end of their admission**

	Died	Survived	p value
Number of VITT cases	20	50	
Demographics			
Median age (IQR)	50 (26)	47 (22)	1.0
Female	12/20 (60%)	27/50 (54%)	0.65
Male	8/20 (40%)	23/50 (46%)	
Clinical assessment			
History of malignancy	1/20 (5%)	1/50 (2%)	0.49
Median admission GCS (IQR)	14 (13-15)	15 (15-15)	<0.0001
Blood biomarkers			
Median lowest platelets (IQR)	30 (21-54)	51 (33-75)	0.034
Median highest D-dimers (IQR)	14172 (10000-35000)	15830 (6050-31301))	0.16
Median admission fibrinogen (IQR)	1.7 (1.1-2.3)	1.7 (1.0-2.5)	0.46
Anti-PF4 antibody positive (%)	14/14 (100)	44/46 (96)	0.43
Neuroradiological biomarkers			
Cerebral infarction	4/20 (20%)	10/50 (20%)	1.0
Any cerebral haemorrhage	15/20 (75%)	26/50 (52%)	0.078
Multiple cerebral haemorrhages	13/20 (65%)	10/50 (20%)	0.0003
Median veins thrombosed (IQR)	3 (1)	3 (2)	0.20
Thrombosis of deep veins	2/20 (10%)	8/50 (16%)	0.71

Results are those which were obtained on admission or as close as possible to admission. For categorical variables, the proportion of patients with the characteristic is shown, followed by the percentage in parenthesis. For continuous variables, the median is shown with the interquartile range (IQR) in parenthesis.

Table A6: **Admission characteristics in patients with VITT-associated CVST who died during admission or who survived and were discharged**

	Numbers of patients treated / not treated	Number of patients that died (%)	p value
Pharmacological			
Any anticoagulation			<0.0001
Yes	60	11 (18%)	
No	10	9 (90%)	
Heparin/LMWH			0.53
Yes	16	3 (19%)	
No	54	17 (31%)	
Non-heparin parenteral anticoagulant			0.0020
Yes	50	9 (18%)	
No	20	11 (55%)	
Direct oral anticoagulant			0.0001
Yes	22	0 (0%)	
No	48	20 (42%)	
Corticosteroid			0.034
Yes	51	11 (22%)	
No	19	9 (47%)	
Anticonvulsant			0.060
Yes	26	22 (85%)	
No	44	28 (64%)	
Fibrinogen replacement			0.051
Yes	15	1 (7%)	
No	55	19 (35%)	
Intravenous immunoglobulin			0.080
Yes	55	13 (24%)	
No	15	7 (47%)	
Plasma exchange			0.13
Yes	16	2 (13%)	
No	54	18 (33%)	
Platelet transfusion			0.0073
Yes	25	12 (48%)	
No	45	8 (18%)	
Invasive			
Endovascular management			0.71
Yes	9	3 (33%)	
No	61	17 (28%)	
Intracranial pressure monitor			0.12
Yes	13	6 (46%)	
No	57	14 (25%)	
Decompressive hemicraniectomy			0.025
Yes	13	7 (54%)	
No	57	13 (23%)	

P values are for chi squared tests comparing the proportion of patients who died during admission, in patients treated compared with those not treated.

Table A7: **Proportions of patients with VITT-associated CVST who died during admission, by treatment modality**

Appendix figures

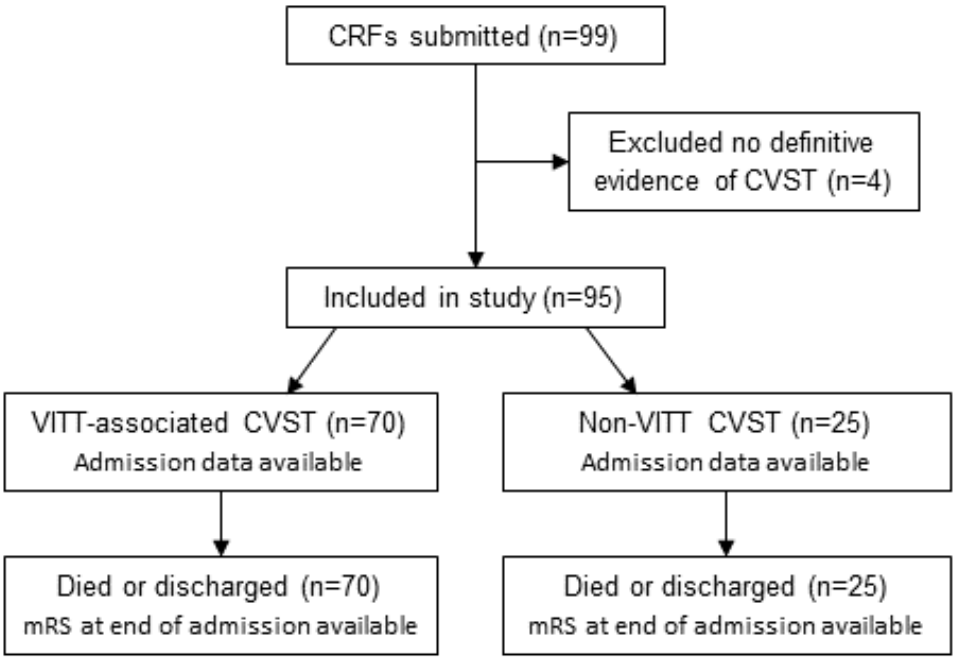

Figure A1: **Study flow diagram**

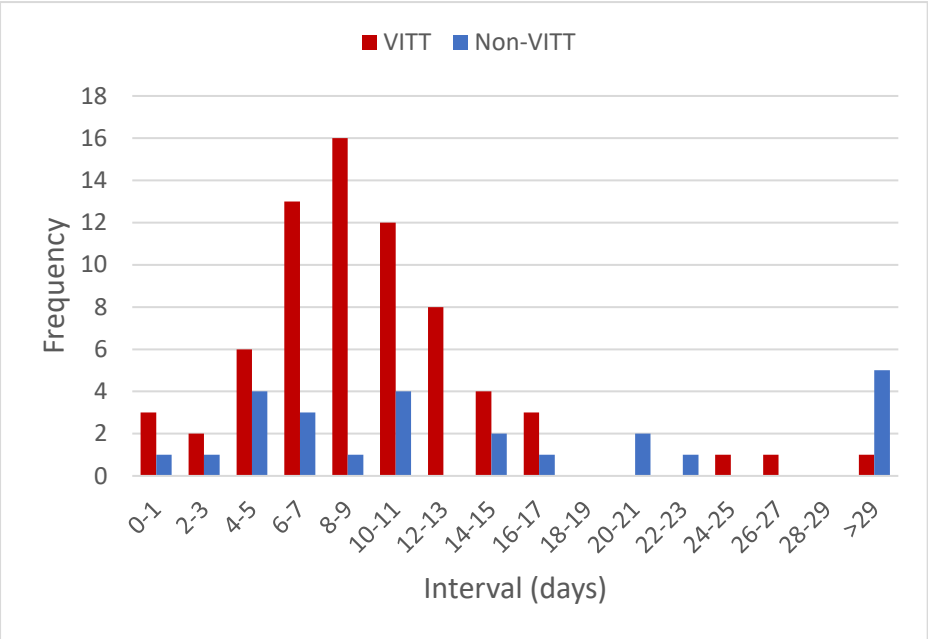

Figure A2: **Interval between vaccine date and onset of symptoms**

Data are shown for all patients with VITT (red bars) or without VITT (blue bars). For patients where a headache developed within hours of vaccination and persisted unchanged up to CVST diagnosis, the onset of that headache was recorded as the CVST symptom onset, even though at the start it most likely had another mechanism.

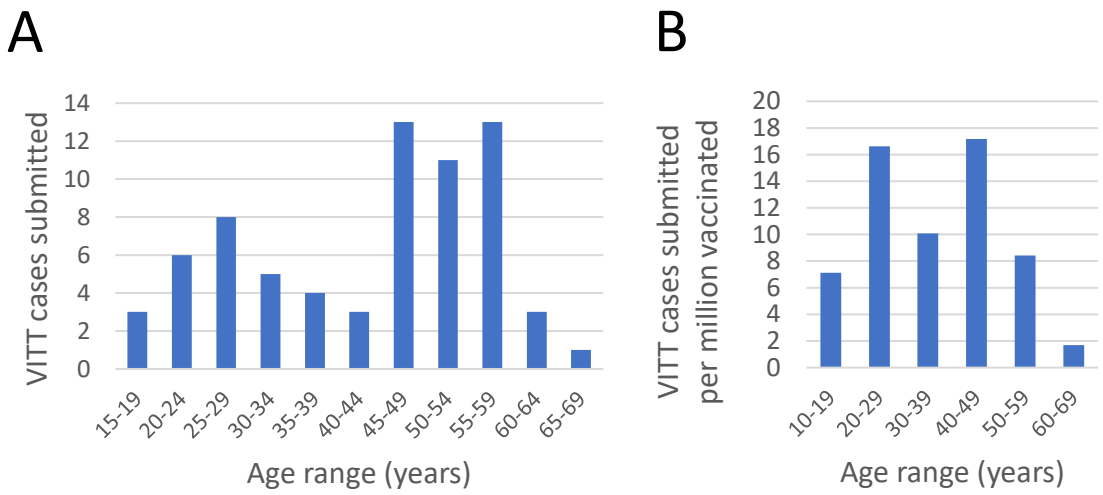

Figure A3: **Age distribution of patients with VITT-associated CVST**

A. Raw data. B. Data adjusted for numbers of patients in each age decade vaccinated in the UK extracted from the OpenSafely data set[13].

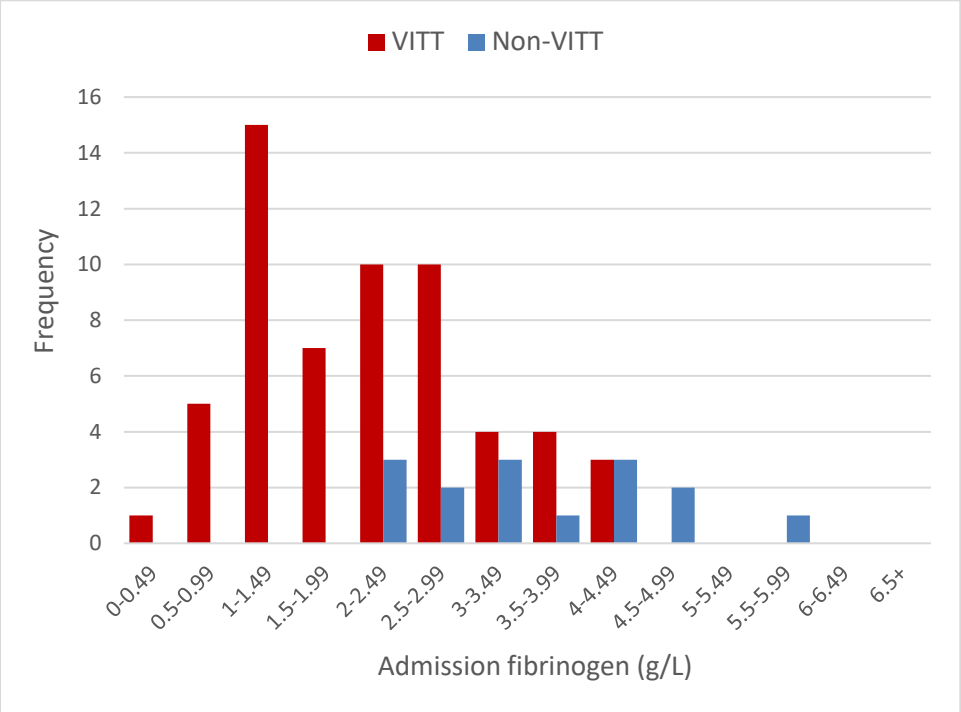

Figure A4: **Distributions of fibrinogen on admission in patients with CVST with and without VITT.**

The median fibrinogen was significantly lower in the VITT group (2.0 g/L) then in the non-VITT group (3.3 g/L, p=0.0001).

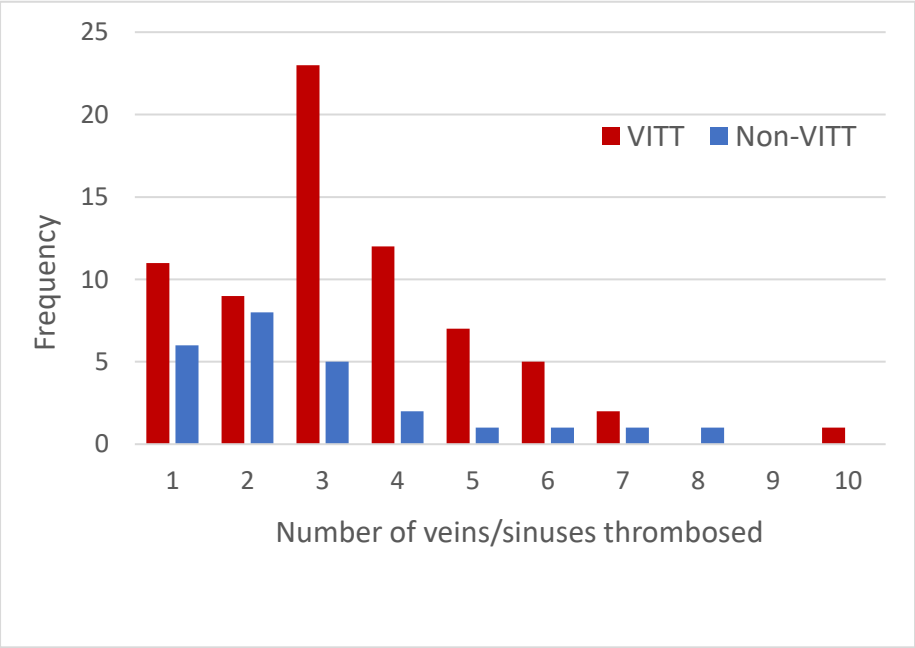

Figure A5: **Number of veins or sinuses thrombosed in the VITT and non-VITT groups**

The median number was higher in the VITT group (3) than in the non-VITT group (2, p=0.04).