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Clinical study

Meaningful use of imaging resources to rule out cerebral venous sinus thrombosis after ChAdOx1 COVID-19 vaccination: Evaluation of the AHA diagnostic algorithm with a clinical cohort and a systematic data review

Philipp Fervers [a,1,*], Jonathan Kottlors [a,1], Thorsten Persigehl [a], Simon Lennartz [a], Volker Maus [b], Sebastian Fischer [b], Hanna Styczen [c], Cornelius Deuschl [c], Marc Schlamann [a], Anastasios Mpotsaris [d], Seraphine Zubel [d], Michael Schroeter [e], David Maintz [a], Gereon Rudolf Fink [e,f], Nuran Abdullayev [a]

[a] Department of Diagnostic and Interventional Radiology, Faculty of Medicine and University Hospital Cologne, University Cologne, Cologne, Germany
[b] Department of Diagnostic and Interventional Radiology, University Hospital Knappschaftskrankenhaus Bochum-Langendreer, University Bochum, Bochum, Germany
[c] Institute for Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany
[d] University Clinic for Neuroradiology, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
[e] Department of Neurology, Faculty of Medicine and University Hospital Cologne, University Cologne, Cologne, Germany
[f] Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Center Jülich, Jülich, Germany

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ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) with cerebral venous thrombosis (CVST) is an improbable (0.0005%), however potentially lethal complication after ChAdOx1 vaccination. On the other hand, headache is among the most frequent side effects of ChAdOx1 (29.3%). In September 2021, the American Heart Association (AHA) suggested a diagnostic workflow to facilitate risk-adapted use of imaging resources for patients with neurological symptoms after ChAdOx1. We aimed to evaluate the AHA workflow in a retrospective patient cohort presenting at four primary care hospitals in Germany for neurological complaints after ChAdOx1. Scientific literature was screened for case reports of VITT with CVST after ChAdOx1, published until September 1st, 2021. One-hundred-thirteen consecutive patients (77 female, mean age 38.7 +/− 11.9 years) were evaluated at our institutes, including one case of VITT with CVST. Further 228 case reports of VITT with CVST are published in recent literature, which share thrombocytopenia (225/227 reported) and elevated d-dimer levels (100/101 reported). The AHA workflow would have recognized all VITT cases with CVST (100% sensitivity), the number needed to diagnose (NND) was 1:113. Initial evaluation of thrombocytopenia or elevated d-dimer levels would have lowered the NND to 1:68, without cost of sensitivity. Hence, we suggest that in case of normal thrombocyte and d-dimer levels, the access to further diagnostics should be limited by the established clinical considerations regardless of vaccination history.

1. Introduction

During the current coronavirus disease (COVID-19) pandemic, immunization by vaccination is expected to curb infection rates and aid in normalizing social life [1,2]. As of March 18th 2021, emergency use authorization has been issued for the three COVID-19 vaccines manufactured by Pfizer-BioNTech®, Moderna®, and Janssen® in the United States, while the European Medicines Agency (EMA) also approved the vaccine Vaxzevria® (ChAdOx1, formerly COVID-19 Vaccine AstraZeneca®) [3,4]. Immunization programs have since been initiated around

* Corresponding author.
E-mail addresses: Philipp.Fervers@uk-koeln.de (P. Fervers), Jonathan.Kottlors@uk-koeln.de (J. Kottlors), Thorsten.Persigehl@uk-koeln.de (T. Persigehl), Simon.Lennartz@uk-koeln.de (S. Lennartz), Volker.Maus@kk-bochum.de (V. Maus), Sebastian.Fischer@kk-bochum.de (S. Fischer), Hanna.Styczen@uk-essen.de (H. Styczen), Cornelius.Deuschl@uk-essen.de (C. Deuschl), Marc.Schlamann@uk-koeln.de (M. Schlamann), Anastasios.Mpotsaris@med.ovgu.de (A. Mpotsaris), Seraphine.Zubel@med.ovgu.de (S. Zubel), Michael.Schroeter@uk-koeln.de (M. Schroeter), David.Maintz@uk-koeln.de (D. Maintz), G.R.Fink@fz-juelich.de (G.R. Fink), Nuran.Abdullayev@uk-koeln.de (N. Abdullayev).
[1] These authors have contributed equally to this work and share first authorship.

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the globe with encouraging results [5]. However, after a series of severe neurological, vascular disorders in temporal association with Vaxzevria®, vaccination has been temporarily suspended in >20 European countries [6].

The New England Journal of Medicine referred to the first reported cases of hypercoagulation in previously healthy individuals after Vaxzevria® as "vaccine-induced immune thrombotic thrombocytopenia" (VITT) [7]. Hematological analysis revealed similar pathophysiological features to heparin-induced thrombocytopenia with the formation of antibodies against platelet antigens, resulting in systemic platelet activation and eventually cerebral venous sinus thrombosis (CVST) or cerebral hemorrhage (CH) [8,9]. VITT primarily occurs in women under 60 years of age within 5 to 24 (median: 10-12) days of vaccination with Vaxzevria® or Janssen®, both based on recombinant adenovirus vectors [8–11]. Only a singular case of VITT is reported after immunization with an mRNA-based vaccine [12]. VITT patients present thromboses at atypical sites (most commonly CVST or portal vein), low platelet counts, and elevated d-dimer levels [11]. The mortality of VITT is significant and ranges from 30% to 60% [11].

VITT with CVST or CH is very rare [8,10]. Merely six cases were documented after administering 6.8 million doses of the Janssen® vaccine (0.00009 % per dose) [10]. As of April 4th 2021, the EMA registered 169 cases of CVST for 34 million vaccinated individuals (0.0005 % per individual) [8]. On the other hand, unspecific headache is among the most common side effects after Vaxzevria®, affecting up to 29.3% of patients after their first vaccination [13,14]. Since the vaccination program's suspension by official authorities has drawn CVST to the center of public awareness, post-vaccination headaches are a common cause of anxiety among recently vaccinated individuals. Subsequently, we observed increasing requests for neuroradiological imaging to exclude CVST in individuals with various neurological symptoms following Vaxzevria® vaccination at our institutes.

Our study's objective was to validate the diagnostic workflow for patients with neurological symptoms after COVID-19 vaccination suggested by the American Heart Association (AHA), aiming to analyze its sensitivity for VITT with CVST as well as the number needed to diagnose (NND) as an indicator for meaningful use of diagnostic resources [15].

2. Materials and methods

All procedures performed in studies involving human participants were conducted following the ethical standards of the 1964 Helsinki declaration and its later amendments. Informed consent was waived by the local review board of the corresponding author's institution (University of Cologne, Faculty of Medicine and University Hospital Cologne, application number 21-1365).

2.1. Patient enrollment

Inclusion criteria to our study comprised.

1) initial presentation at the emergency department due to neurological symptoms within four weeks of ChAdOx1 vaccination, qualifying for imaging and a complete blood count as per AHA criteria (new severe headache, subacute encephalopathy, visual loss, seizure, or focal neurological deficit) [15];
2) neuroradiological imaging at one of the following four participating centers: Center A (13th March – 10th June 2021), B), Center A, B, and C (13th March – 15th May 2021);
3) patient age $\geq$ 18 years.

Exclusion criterium was.

1) history of chronic medical conditions consistent with the symptoms at hospital presentation (n = 1 patient presenting with headache and history of therapy-resistant migraine).

2.2. External validation

A systematic PubMed® research was performed for identification of previously published, in detail VITT case reports after ChAdOx1. The research was performed by the term "(vaccine-induced thrombotic thrombocytopenia OR VITT OR post-vaccination OR after vaccination) AND (CVT OR CVST OR cerebral venous thrombosis OR sinus thrombosis)" on September 1st, 2021.

Inclusion criteria to the systematic database review comprised.

1) original report of a VITT case with CVST after ChAdOx1;
2) publication in English language;
3) publication after January 1st, 2021, following the beginning of the COVID-19 vaccination campaign.

Exclusion criteria were.

1) lack of originally reported VITT cases or overlap with previously published patients without explicit identification of the original cases;
2) report of VITT with CVST in absence of ChAdOx1.

The AHA algorithm was applied retrospectively to the retrieved case reports in a similar fashion as performed for our clinical cohort.

2.3. Assessment of clinical data

Individual neurological symptoms were noted based on the emergency department's initial report. We reviewed the medical records for a history of pre-existing medical conditions. Laboratory results were assessed based on initial blood tests.

2.4. Image acquisition and evaluation

After evaluation of patient history and clinical assessment by the respective neurology department, diagnostic imaging was initiated as magnetic resonance imaging (MRI) or computed tomography (CT), based on clinical suspicion, urgency, and device availability. Imaging protocols are illustrated in detail in supporting information S1. All imaging procedures were performed for clinical indications. Images were analyzed in consensus by two radiologists with at least three years of experience in neuroradiology at each center, respectively.

3. Statistical assessment

Statistical analysis was performed in the R language for statistical computing, R Foundation, Vienna, Austria, version 4.0.0. Normally distributed data are reported as mean $\pm$ standard deviation. Non-normally distributed data are reported as median [interquartile range].

4. Results

One-hundred-thirteen consecutive patients matched our eligibility criteria (77 female, 36 male). The mean patient age was 38.7 $\pm$ 11.9 years, ranging from 18 $-$ 72 years. In all patients, imaging was performed on the day of clinical presentation with a median of 9.0 [6.0–14.0] days after vaccination.

Most commonly performed was contrast-enhanced MRI (71 cases), followed by contrast-enhanced CT (23 cases), unenhanced MRI with phase-contrast angiography (14 cases), and unenhanced CT (five cases).

The most frequently reported symptom in clinical assessment was new severe headache (95/113, 84%). Fifty-eight patients (51%) suffered from further neurological symptoms, most commonly abnormal sensations, including hypoesthesia and dysesthesia (24/113, 21%), as well as dizziness (14/113, 12%), visual impairment (13/113, 12%), or word-finding difficulties (4/113, 4%). Three patients presented with

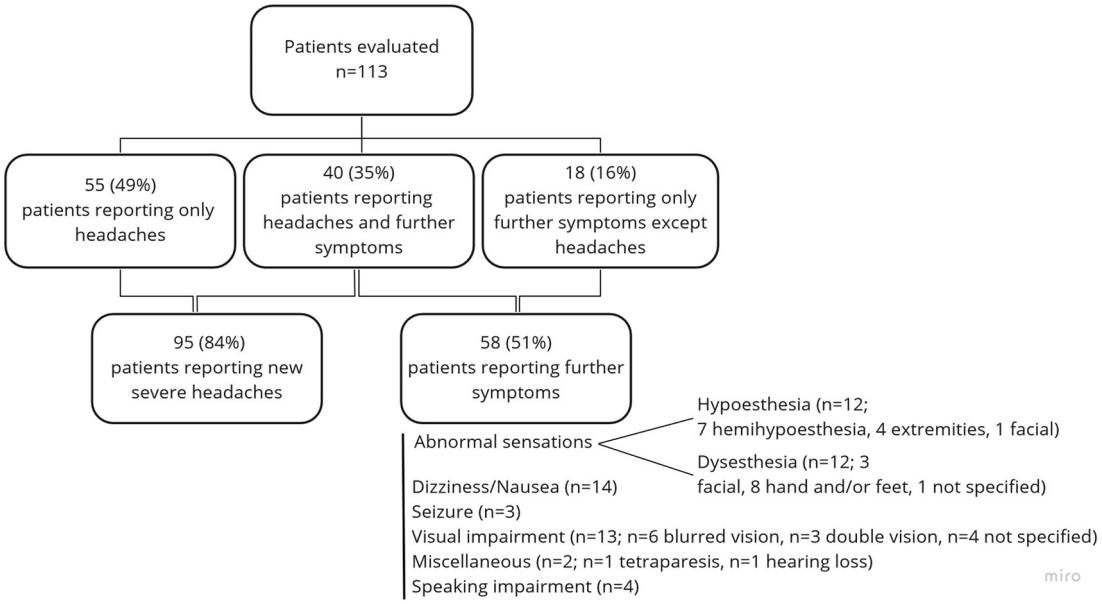

Fig. 1. Clinical symptoms at initial presentation of patients that qualified for neuroradiological imaging after Vaxzevria®.

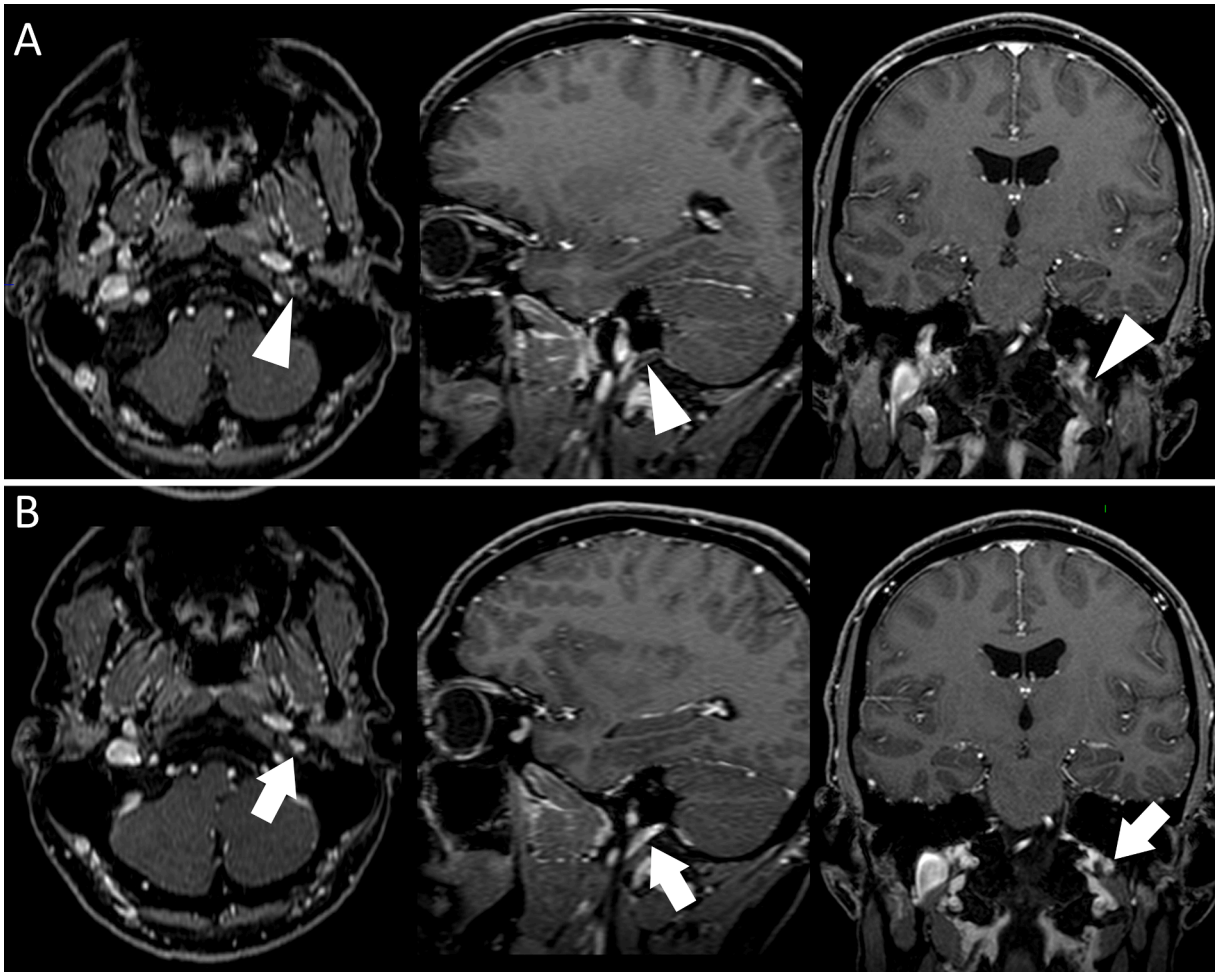

Fig. 2. Thrombosis of the distal left sigmoid sinus after Vaxzevria® vaccination.

seizures (3%), one patient with tetraparesis (1%). Symptoms at the initial presentation are illustrated in Fig. 1.

In most cases, the final diagnosis concluded an unspecific or idiopathic condition (96/113, 85%). One Guillain-Barré syndrome was reported without prior infection history, which was hence attributed to the prior vaccination [16]. The singular patient presenting with

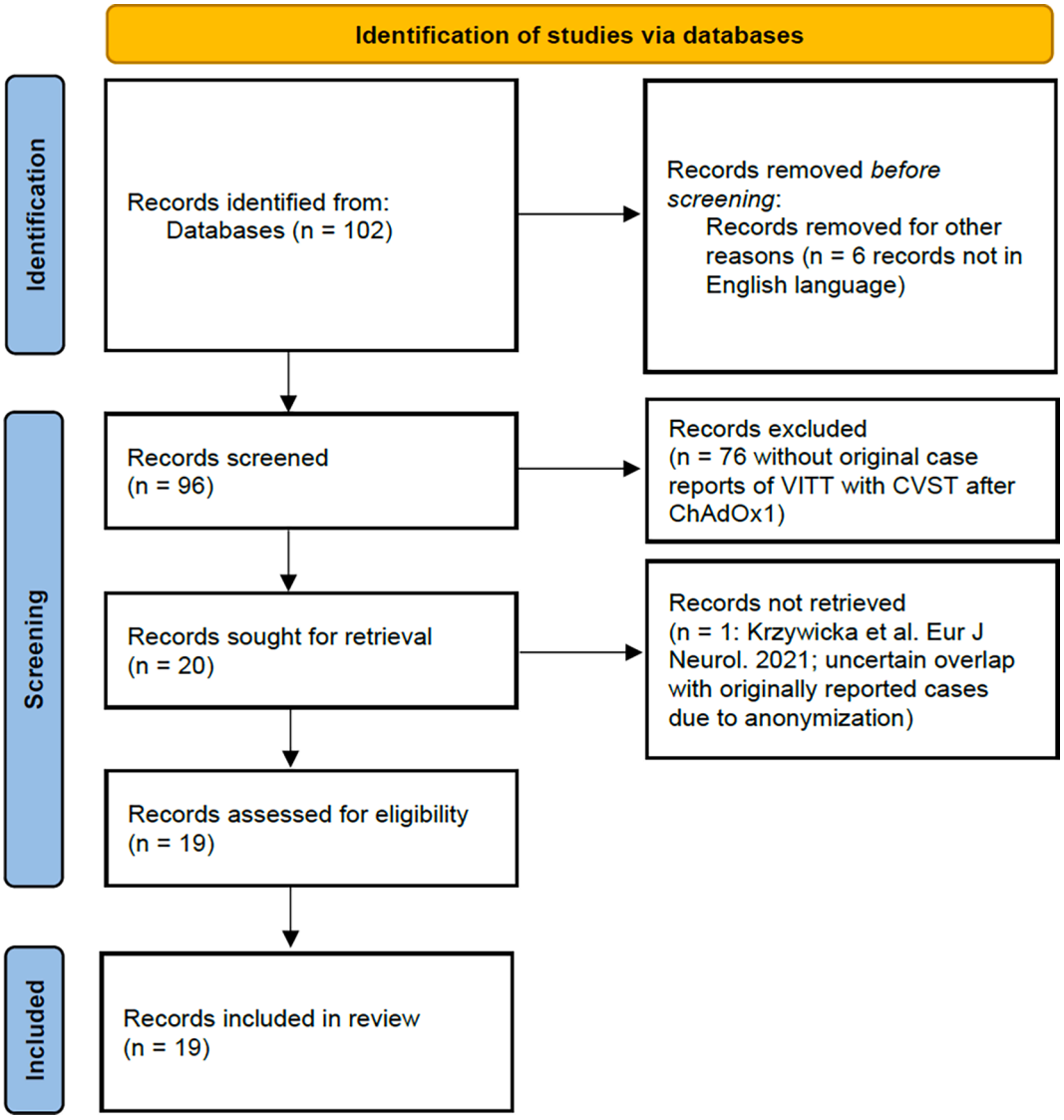

Fig 3. PRISMA flow diagram of the performed systematic literature research.VITT: vaccine-induced immune thrombotic thrombocytopenia; CVST: cerebral venous sinus thrombosis.

tetraparesis suffered from VITT with distal aortal thrombosis (Leriche syndrome), considered a side effect of vaccination. This patient underwent a head MRI for exclusion of CVST without initial evidence of distinct neurological symptoms. The abdominal thrombus was retrieved in a combined endovascular and surgical approach. Further, intravenous immunoglobulins and arbogatran were administered intravenously. At clinical follow-up after two months, the patient did not present any perfusion deficit of the lower extremity.

One patient that was included was diagnosed with VITT and CVST. After immediate transfer to our stroke unit, we initiated therapy with intravenous immunoglobulins and thrombin inhibition with arbogatran. Twelve days after initial presentation, the patient was dismissed from the hospital with mildly decreased thrombocyte count (142.000/µl) and oral anticoagulation (pradaxa). A follow-up MRI at three months after the first imaging confirmed successful therapy of the thrombosis (Fig. 2). The patient did not maintain any neurological deficit.

The 37 years old male patient presented at our emergency department with a history of recent Vaxzevira® vaccination, therapy-resistant headaches, thrombocytopenia (22.000/µl), and elevated d-dimer levels (>35.2 mg/l). The contrast-enhanced MRI scan demonstrated a filling defect in the left sigmoid sinus (arrowheads) (A). Positive anti-PF4/heparin ELISA results validated vaccine-induced thrombotic thrombocytopenia. A follow-up MRI after three months confirmed

Table 1
Patients requiring specific diagnostics or therapy (22/113, 19%).

Condition	Number of cases
First generalized seizure	n = 3
Allergic exanthema	n = 3
Vaccine-induced thrombotic thrombocytopenia	n = 2
Neuropathia vestibularis	n = 2
Idiopathic hearing loss	n = 1
Hypertensive crisis	n = 1
Guillain-Barré syndrome	n = 1
Benign paroxysmal positional vertigo	n = 1
Pulmonary embolism without thrombocytopenia	n = 1
Mild thrombocytopenia with unknown cause, final diagnosis not established	n = 7

Both VITT cases that we observed initially presented with thrombocytopenia and elevated d-dimer levels. Concerning the non-VITT patients, thrombocyte levels were decreased in 5/108 (5%), and d-dimer levels were elevated in 68/101 (67%) cases. All seven patients with thrombocytopenia also presented elevated d-dimer levels. Patient details are summarized in Table 2.

Table 2
Patient details.

Parameter	Reported observations	Non-VITT cases (n = 111)	VITT case #1	VITT case #2
Age [years]	113/113 (100%)	38.5 ± 11.8	37	63
Sex [F/M]	113/113 (100%)	77/34	0/1	0/1
Days between vaccination and imaging	113/113 (100%)	9 [6–14]	10	14
First / Second dose of Vaxzevria®	113/113 (100%)	95/16	1/0	1/0
C-reactive protein (normal: <5 mg/dl)	107/113 (95%)	0.9 [0.6–1.9] (14/107, 13% >5)	30.4	6.4
D-dimer (normal: <0.2 mg/l)	101/113 (89%)	0.3 [0.2–0.6] (68/101, 67% >0.2)	>35.2	2.8
Platelets (normal: 150–450 /nl)	108/113 (96%)	254 [224–309] (7/108, 6% ⟨150)	63	22
Leucocyte count (normal: 4.5–11.0 /µl)	109/113 (96%)	6.6 [45.6–8.2] (0/109, 0% >11.0)	8.1	11.1
Site of thrombosis			Left sigmoid sinus	Distal abdominal aorta

The PubMed® research by the above specified criteria yielded 102 results, including 19 publications with a total of 227 in detail case reports of vaccine-induced immune thrombotic thrombocytopenia (VITT) with cerebral venous sinus thrombosis (CVST) after Vaxzevria®. A PRISMA diagram illustrates the results of our systematic literature research (Fig. 3) [17].

successful therapy of the thrombosis (B) (Fig. 3).

All patients requiring further diagnostics or therapy (22/113, 19%) are summarized in Table 1, including both of the above introduced patients that met the criteria for VITT (Table 2).

Patient details of externally reported cases are summarized in Table 3.

Almost all externally reported cases presented with thrombocytopenia (99%, 225/227) and elevated d-dimer levels (99%, 100/101). A combination of physical examination and assessment of patient history allowed for pre-selection of VITT with CVST for neuroradiological imaging in 21/23 (91%) of reported cases.

5. Discussion

After a series of severe CVSTs and cerebral hemorrhage associated with Vaxzevria® vaccination, immunization with the adenovirus vector vaccine had been temporarily suspended in several European countries. In their final report concerning these events, the EMA concluded to list CVST as a rare Vaxzevria® side effect [8]. Even though VITT occurs very rarely (169 cases of CVST in 34 million vaccinated individuals in Europe), it is in the spotlight of current public awareness [8,38]. Concerns have risen that due to extensive media coverage, the risk for severe post-vaccination complications such as VITT with CVST is overestimated by large parts of the population. The topic is further relevant as adenovirus vaccines are crucial for the immunization programs throughout low- and middle-income countries since they do not require ultra-cold chain storage [37]. A shortage of neuroradiologic resources in these countries, with large parts of their young population still waiting for their COVID vaccination, underlines the urgency of a simple diagnostic workflow for neurologically symptomatic patients after Vaxzevria®.

In this study, we evaluated the diagnostic algorithm for guiding imaging assessment of patients with VITT and CVST, as suggested by the AHA. 112/113 neuroradiological imaging studies included from our centers undergone by mostly young individuals did not show any signs of CVST, whereas one patient was diagnosed with VITT and CVST. *Vice versa*, the number of neuroradiological exams needed to diagnose (NND) one VITT with CVST following AHA suggestions at our institutes was 1:113. Applied retrospectively, the AHA algorithm would have detected the 228 cases of recently published case reports of VITT with CVST, including the singular case at our institute.

The relatively high NND demonstrates that resource-sparing diagnosis of VITT and CVST is still challenging. Uncomplicated headache is reported by up to 29.3% of individuals after their first Vaxzevria® dose. Accordingly, post-vaccination headaches do not qualify as a specific marker for VITT (0.0005% per individual) [8,13,14,39,40]. Yet, headaches might be the only symptom in individuals with early VITT and CVST, and hence warrant further investigation [18,23,30,36]. Headaches are also the most common symptom of CVST without thrombocytopenia [41]. The AHA algorithm acknowledges this dilemma by allowing low-threshold access to a full blood count and concurrent neuroradiological imaging – a patient with new severe headaches < 4 weeks after vaccination qualifies for blood tests and imaging [15]. A previously published diagnostic flow chart by the International Society of Thrombosis and Haemostasis from April of 2021 equally recommends concurrent blood tests and imaging solely based on clinical suspicion [42].

Other authors proposed thrombocytopenia < 150 /nl or elevated d-dimer levels as a gatekeeper for venous CT- or MRI-angiography in the context of post-vaccination headaches [37]. This would have lowered the NND in our cohort to 1:68, whilst maintaining a retrospective sensitivity of 100% throughout the internationally published VITT with CVST cases. Since CVST is more severe when occurring due to VITT, minimal CVST without VITT might not comply with the "severe headache" criterium of the AHA workflow [29,43]. Patients with CVST due to VITT regularly present in a severe condition with high rates of cerebral hemorrhage and brain herniation in approximately half of the cases, demanding for neuroradiological imaging [44]. Initial access to a laboratory test including d-dimer levels might help to identify the patients presenting for minimal CVST without VITT and less pronounced clinical findings. CVST without VITT during the 28 day period after vaccination is even rarer than CVST with VITT (0.1/100,000 vs. 2.5/100,000) [45]. Yet, a recent study suggests that the risk of CVST without VITT might as well increase after vaccination with ChAdOx1 [46]. This assumption might be limited by underreporting of thrombocytopenia especially in early VITT cases [46]. Nevertheless, an early negative d-dimer test excludes CVST with a negative predictive value of 99.6% and might help to lower the NND [43].

Neurologists should first rule out VITT when managing post-vaccination patients with neurological symptoms [9,47]. All 228 comprehensively reported VITT cases with CVST in up-to-date literature could be recognized by either thrombocytopenia or elevated d-dimers, which the data suggest a highly sensitive and readily available screening tool (Table 3). An elevated d-dimer level combined with headaches but without thrombocytopenia might hint at CSVT without VITT, yet is a typical clinical pattern that demands neuroradiological imaging. Hence, we attribute our study's high ratio of patients with elevated d-dimers to a selection bias (67%).

After an initial evaluation, individuals with low platelet count should be admitted as an inpatient with suspicion of VITT and low-threshold access to medical imaging [47]. In particular, younger women require careful examination since most cases of VITT were observed in this group; given any uncertainties, an unenhanced MRI with venous phase-contrast angiography should be discussed. Antibodies against platelet factor 4 confirm the diagnosis [24]. Further management of VITT patients requires interdisciplinary care to exclude other atypical

Table 3
Case reports of vaccine-induced thrombotic thrombocytopenia with cerebral venous sinus thrombosis after Vaxzevria®.

Author, region, number of VITT cases	Median age (range)	Sex (F:M)	Time from vaccination to onset	Number of CVST cases	Anamnestic and physical examination neurological findings other than a headache	Elevated D-dimer levels	Thrombocytopenia
Esba et al., Saudi Arabia, n = 4 [18]	51 (27–61)	2:2	6–14 days	2	1/2 (impaired vision, disorientation)	NA	2/2
Tolboll Sorensen et al., Denmark, n = 1 [19]	30	1:0	8 days	1	1/1 (ecchymosis)	1/1	1/1
Greinacher et al., Germany, n = 11 [20]	26 (22–49)	9:2	6–16 days	9	NA	6/6	9/9
Wolf et al., Germany, n = 3 [21]	36 (22–46)	3:0	7–17 days	3	3/3 (seizure; hemianopia and aphasia; somnolence and hemiparesis)	3/3	3/3
Tiede et al., Germany, n = 5 [22]	61 (41–67)	5:0	5–11 days	1	1/1 (somnolence, dysphasia, hemiparesis, arterial hypertension)	1/1	1/1
Schultz et al., Norway, n = 5 [23]	39 (32–54)	4:1	7–10 days	4	3/4 (fever and visual disturbances; drowsiness; hemiparesis)	4/4	4/4
Scully et al., United Kingdom, n = 23 [24]	46 (21–77)	14:9	6–24 days	13	NA	13/13	13/13
Mehta et al., United Kingdom, n = 2 [25]	25, 32	0:2	6 and 9 days	2	2/2 (hemiparesis; petechiae, gum bleeding, hemiparesis and hemisensory loss)	NA	2/2
Castelli et al., Italy, n = 1 [26]	50	0:1	9 days	1	1/1 (loss of strength lower extremity, visual impairment)	1/1	1/1
D'Agostino et al., Italy, n = 1 [27]	54	1:0	12 days	1	1/1 (hemisyndrome)	1/1	1/1
Jamme et al., France, n = 1 [28]	69	1:0	11 days	1	1/1 (mydriasis, loss of consciousness)	NA	1/1
Perry et al., United Kingdom, n = 70 [29]	47 (IQR 32–55)	39:31	9 days (IQR 7–12)	70	NA	61/62	69/70[#]
Guan et al., Taiwan, n = 1 [30]	52	0:1	10 days	1	none	1/1	1/1
Bonato et al., Italy, n = 1 [31]	26	1:0	14 days	1	1/1 (hemisyndrome)	1/1	1/1
Choi et al., Korea, n = 1 [32]	33	0:1	9 days	1	1/1 (dysarthria, hemiparesis)	1/1	1/1
Wiedmann et al., Norway, n = 6 [33]	43	3:0	7 days	3*	3/3 (hemisyndrome; hypoesthesia, visual impairment; abdominal pain)	3/3	3/3
Pavord et al., United Kingdom, n = 220 [34]	48 (18–79)	119:98 (217 reported)	14 (5–48) days	110	NA	NA	109/110[#]
Bano et al., United Kingdom, n = 3 [35]	53, 55	1:1	8, 11 days	2	2/2 (dysphasia, monoparesis and discoordination; facial paresis)	2/2	2/2
Ikenberg et al., Germany, n = 1 [36]	30–39	1:0	7 days	1	none	1/1	1/1

Case reports are partially included from the review by Thakur et al. [37].
*two further patients were previously reported by Schultz et al.
[#]two patients were diagnosed with VITT and CVST despite normal platelet levels by Perry et al. (headache, dysphasia, and elevated d-dimer) and Pavord et al. (elevated d-dimer).
NA, not reported; IQR, interquartile range.

thromboembolic events and specialized therapy, which is described elsewhere [37].

Conversely, after ruling out thrombocytopenia, elevated d-dimer levels, and focal neurological deficits, we suggest that the differential diagnosis VITT with CVST can be rejected and does not demand further exclusion by neuroradiological imaging [48,49]. In particular, we conclude that unspecific headache as a common side-effect of Vaxzevria® does not require medical imaging; contrarily, diagnostic resources are depleted on young, healthy individuals without achieving a higher pre-test probability. The suggested modified AHA workflow is summarized in Fig. 4.

The original AHA algorithm for diagnosis of VITT with CVST (a) recommends concurrent blood tests and neuroradiological imaging based on clinical suspicion [15]. Modification of the algorithm (b) by low-threshold access to a blood count and d-dimer assessment helps to enable a higher pre-test probability for consecutive imaging. Since the VITT with CVST cases in recent literature presented thrombocytopenia and/or elevated d-dimers, the differential diagnosis can be safely rejected with normal thrombocyte and d-dimer levels. The number of neuroradiological exams to diagnose one VITT with CVST was 1:113 for the original algorithm (a) and 1:68 for the modified algorithm (b), both yielding a perfect sensitivity of 100%.

If a patient qualifies for neuroradiological assessment, both contrast-enhanced MRI and venous CT angiography can equally demonstrate a filling defect in a venous sinus [50]. However, for detection of cortical vein thrombosis and parenchymal damage as a complication of CVST, MRI is more sensitive [50]. Due to the minimal number of expected positive examinations, MRI should generally be the modality of choice to minimize accumulative radiation dose.

Limitations of our study include its retrospective design and the relatively small patient population. Further, the systematic database review might be limited by the search terms and language of our query. Our small case series does not allow for considerations about the likelihood of an adverse event with the exceptionally low probability of 0.0005%, or the exact NND to detect such event. This issue can only be addressed by centralized, large-scale databases for adverse reactions (e.g., EudraVigilance in Europe).

Our study investigated a resource-sparing, yet sensitive approach to diagnose VITT with CVST after ChAdOx1 vaccination. We conclude that the established clinical findings should be combined with initial evaluation of thrombocyte and d-dimer levels to indicate neuroradiological imaging.

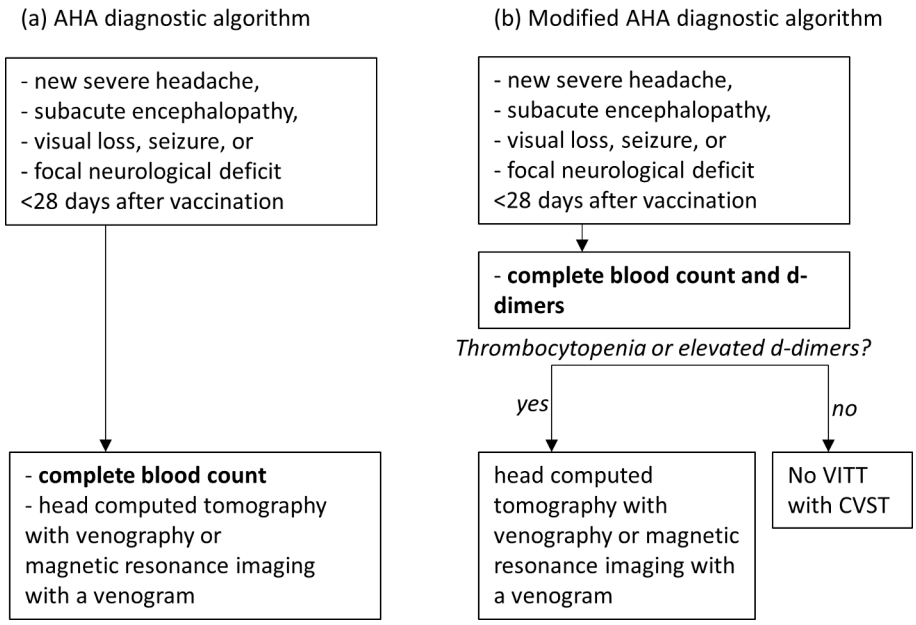

Fig. 4. Risk-adapted diagnosis of vaccine-induced thrombotic thrombocytopenia (VITT) with cerebral venous sinus thrombosis (CVST).

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DM is on the speaker's bureau of Philips Healthcare. AM is a consultant for Stryker, Perflow, Phenox and Balt. SF is a consultant for Microvention. MS received personal honoraria from Alexion, Biogen, Gilead, Roche, and Sanofi. All other authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2022.05.031.

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