

median titer was lower by a factor of 1.5 against the BA.2.12.1 subvariant and by a factor of 2.9 against the BA.4 or BA.5 subvariant.

These data show that the BA.2.12.1, BA.4, and BA.5 subvariants substantially escape neutralizing antibodies induced by both vaccination and infection. Moreover, neutralizing antibody titers against the BA.4 or BA.5 subvariant and (to a lesser extent) against the BA.2.12.1 subvariant were lower than titers against the BA.1 and BA.2 subvariants, which suggests that the SARS-CoV-2 omicron variant has continued to evolve with increasing neutralization escape. These findings provide immunologic context for the current surges caused by the BA.2.12.1, BA.4, and BA.5 subvariants in populations with high frequencies of vaccination and BA.1 or BA.2 infection.

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SARS-CoV-2 Infection in Patients with a History of VITT

TO THE EDITOR: Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a prothrombotic adverse effect of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an important measure in the prevention of severe coronavirus disease 2019 (Covid-19). VITT is caused by platelet-activating antiplatelet factor 4 (PF4) antibodies of immunoglobulin G class that have been rarely induced by two adenovirus vector-based Covid-19 vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen).¹

All available Covid-19 vaccines generate an immune response against the SARS-CoV-2 spike protein, which arouses concern that VITT may be triggered by cross-reactivity between PF4 and spike protein,² a view that has been reinforced by the detection of antibodies against PF4 in some patients with Covid-19.³ Despite encouraging in vitro studies that provided no evidence of a link between anti-SARS-CoV-2 and anti-PF4 immune responses,⁴ investigators could not provide in vivo evidence to exclude such a link due to the lack of an animal model. However, if both

immune responses are indeed linked, VITT survivors who subsequently contract Covid-19 should have an increase in anti-PF4 antibodies, potentially even retriggering thrombocytopenia or thrombosis.

We performed periodic evaluation of VITT antibody status (study registry, EUPAS45098) in a cohort of 69 patients with a history of VITT who had received an adenovirus vector Covid-19 vaccine. Of these patients, 24 did not receive any subsequent doses of a Covid-19 vaccine; the remaining 45 patients received subsequent doses of a messenger RNA (mRNA) vaccine (either the BNT162b2 [Pfizer-BioNTech] or the mRNA-1273 [Moderna] vaccine). Of these patients, 31 received a second dose and 14 received a third dose. The characteristics of the patients are provided in Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org. Of the 69 patients, Covid-19 developed in 11 (16%), all of whom had mild symptoms (Table 1). Covid-19 occurred more frequently in the patients who had received only the adenovirus vector vaccine than in those who had subsequently

Table 1. Characteristics of 11 Patients with a History of VITT with Subsequent Covid-19.*

Patient No.	Age in Yr, Sex	Clinical VITT Presentation	Vaccine Doses before Covid-19 <i>number</i>	Time from VITT to Covid-19	Anti-PF4-Antibody Status† <i>value (time)</i>	Anticoagulation at Covid-19 Onset
1	34, M	DVT	2	7 mo	Before Onset of Covid-19: 3.27; PAA positive (28 wk) After Recovery from Covid-19: 2.26; PAA negative (8 wk)	None
2	41, M	CVST, portal-vein thrombosis, left jugular-vein thrombosis	1	10 mo	1.97; PAA positive (16 wk)	Apixaban (5 mg twice daily)
3	48, M	Arterial stroke	1	3 mo	1.81; PAA negative (3 wk)	Aspirin (100 mg) plus apixaban (2.5 mg) twice daily
4	53, F	CVST, DVT	1	10 mo	1.72; PAA negative (5 days)	None
5	51, F	Thrombocytopenia, elevated D-dimer, headache ("pre-VITT")	1	12 mo	1.26; PAA negative (3 wk)	Rivaroxaban (20 mg once daily)
6	36, M	CVST	3	9 mo	0.77; PAA negative (4 wk)	Dabigatran (150 mg twice daily)
7	52, F	Pulmonary embolism	1	14 mo	0.97; PAA negative (5 wk)	None
8	31, F	Thrombocytopenia, elevated D-dimer, headache ("pre-VITT")	2	10 mo	0.28; PAA negative (10 wk)	None, then dalteparin (5000 U daily) for 6 wk post-partum
9	31, M	CVST	1	12 mo	0.85; PAA negative (1 wk)	None
10	40, M	CVST	1	9 mo	0.59; PAA positive (1 wk)	Phenprocoumon (INR adjusted)
11	31, F	CVST with secondary hemorrhage	2	13 mo	0.35; PAA negative (6 wk)	None

* All 11 patients with a history of vaccine-induced thrombotic thrombocytopenia (VITT) had mild symptoms of Covid-19 resembling the common cold (e.g., fever, rhinitis, headache, cough, and chills). CVST denotes cerebral venous sinus thrombosis, DVT deep-vein thrombosis, F female, INR international normalized ratio, and M male.

† Testing for anti-PF4-antibody status was performed by means of enzyme-linked immunosorbent assay. Results are shown in optical density units (negative test result, <0.50 units). In 8 of the patients, the initial test for PF4-enhanced platelet activation on a platelet-activation assay (PAA) was positive, and subsequent testing in the last sample obtained before Covid-19 infection was negative; none of the 8 patients had positive results on this assay again after Covid-19 infection. The course of the anti-PF4 antibody response in the patients is shown in Figure S1 in the Supplementary Appendix.

received one or two doses of an mRNA vaccine (7 of 24 patients [29%] vs. 4 of 45 patients [9%]; $P=0.04$ by Fisher's exact test). This lower frequency of symptomatic Covid-19 supports the concept of offering patients with a history of VITT subsequent vaccination with an mRNA-based SARS-CoV-2 vaccine.⁵

In all the patients who had contracted Covid-19, a follow-up blood sample that was obtained after their recovery was available at a median of 2 weeks after the onset of infection. No major increases in PF4-antibody levels developed after recovery from Covid-19. In most of the patients, repeat optical density readings were lower than those in the last sample obtained before the onset of Covid-19, a finding that was consistent with the inherent natural decline in anti-PF4 antibodies.⁵ No patient had recurrent thrombocytopenia, new or recurrent thrombosis, or reversion to a positive platelet-activation assay. Our observations provide *in vivo* evidence that corroborate our previous *in vitro* findings⁴ that the immune responses against the SARS-CoV-2 spike protein (induced by Covid-19 or any of the Covid-19 vaccines) and against PF4 (induced in association with VITT) are independent. Our finding that Covid-19 does not restimulate anti-PF4 antibodies in patients with a history of VITT provides further insights into the pathogenesis of this disorder and may be helpful in counseling patients regarding further Covid-19 vaccination with an mRNA vaccine.

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Nonoperative or Surgical Treatment of Acute Achilles' Tendon Rupture

TO THE EDITOR: Myhrvold et al. (April 14 issue)¹ report the use of heel wedges as part of their treatment algorithm. However, it is increasingly recognized that the wedges promote neither ankle equinus nor tendon apposition but rather tend to elicit flexion at the midfoot.^{2,3} Indeed, Figure 4 in the protocol of their article (available at NEJM.org) shows this very midfoot pseudo-equinus effect, which may account for the markedly high percentage of patients with repeat rupture in the group that received nonoperative treatment in this trial as compared with analogous studies in which nonoperative therapy was used in conjunction with either expeditious ankle mobilization or weight-bearing or both.⁴ The au-

thors note that the literature regarding repeat rupture after accelerated nonoperative functional rehabilitation is conflicting, with some studies reporting high rates and others low rates equivalent to those associated with surgical repair. It is of interest that studies in which nonsurgical rehabilitation has been found to be associated with high rates of repeat rupture, cited by the authors, are characterized by the use of heel wedges rather than orthoses, which affect veritable ankle plantar flexion and equinus.^{5,6} The use of wedges in the trial conducted by Myhrvold et al. may have had disproportionate adverse effects on patients undergoing nonsurgical treatment, given that tendon apposition depends more on ankle