Table 1. Symptomatic SARS-CoV-2 Infection and mRNA Vaccine Effectiveness among UCSDH Health Workers, March through July 2021.*

	March	April	May	June	July
UCSDH workforce — no. of persons	18,964	18,992	19,000	19,035	19,016
Vaccination status — no. of persons					
Fully vaccinated†	14,470	15,510	16,157	16,426	16,492
mRNA-1273 (Moderna)	6,608	7,005	7,340	7,451	7,464
BNT162b2 (Pfizer–BioNTech)	7,862	8,505	8,817	8,975	9,028
Unvaccinated	3,230	2,509	2,187	2,059	1,895
Percentage of workers fully vaccinated	76.3	81.7	85.0	86.3	86.7
Symptomatic Covid-19					
Fully vaccinated workers	3	4	3	5	94
Unvaccinated workers	11	17	10	10	31
Percentage of cases in fully vaccinated workers	21.4	19.0	23.1	33.3	75.2
Attack rate per 1000 (95% CI)					
Fully vaccinated workers	0.21 (0.21–0.47)	0.26 (0.26–0.50)	0.19 (0.21–0.40)	0.30 (0.31–0.53)	5.7 (5.4–6.2)
Unvaccinated workers	3.4 (2.1–5.9)	6.8 (4.5–10.6)	4.6 (2.6–8.2)	4.9 (2.9–8.7)	16.4 (11.8–22.9)
Vaccine effectiveness — % (95% CI)	93.9 (78.2–97.9)	96.2 (88.7–98.3)	95.9 (85.3–98.9)	94.3 (83.7–98.0)	65.5 (48.9–76.9)

* UCSDH denotes University of California San Diego Health.
† Data are the total number of workers who had received two doses of an mRNA vaccine as of the last day of the month.

1. Keehner J, Abeles SR, Torriani FJ. More on SARS-CoV-2 infection after vaccination in health care workers. reply. N Engl J Med 2021;385(2):e8.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.
3. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Six month safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. July 28, 2021 (https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1). preprint.
4. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385:585-94.
5. Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. August 5, 2021 (https://www.medrxiv.org/content/10.1101/2021.08.03.21261496v1). preprint.

DOI: 10.1056/NEJMc2112981

Myocarditis after Covid-19 mRNA Vaccination

TO THE EDITOR: The Centers for Disease Control and Prevention recently reported cases of myocarditis and pericarditis in the United States after coronavirus disease 2019 (Covid-19) messenger RNA (mRNA) vaccination.[1] In recently published reports, diagnosis of myocarditis was made with the use of noninvasive imaging and routine laboratory testing.[2-5] Here, we report two cases of histologically confirmed myocarditis after Covid-19 mRNA vaccination.

Patient 1, a 45-year-old woman without a viral prodrome, presented with dyspnea and dizziness 10 days after BNT162b2 vaccination (first dose). A nasopharyngeal viral panel was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A and B, enteroviruses, and adenovirus (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). A serum polymerase-chain-reaction (PCR) assay and serologic tests showed no evidence of active parvovirus, enterovirus, human immunodeficiency virus, or infection with SARS-

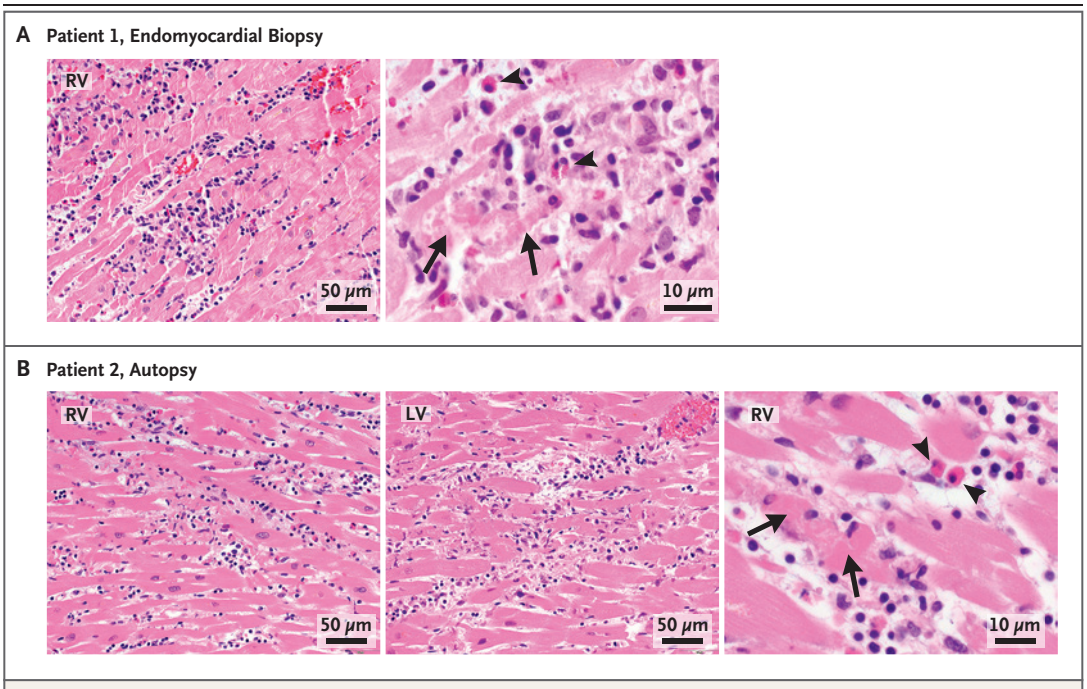

Figure 1. Histopathological Findings from Endomyocardial Biopsy and Autopsy.

Hematoxylin–eosin stains of heart-tissue specimens obtained by means of endomyocardial biopsy in patient 1 (Panel A) and autopsy in patient 2 (Panel B) showed myocarditis in both patients, with multifocal cardiomyocyte damage (arrows) associated with mixed inflammatory infiltration. Scattered eosinophils were noted (arrowheads). The images of the hematoxylin–eosin stains were obtained with 10× eyepieces and 40× or 60× objectives. Additional information is provided in the Supplementary Appendix. RV denotes right ventricle, and LV left ventricle.

CoV-2. At presentation, she had tachycardia; ST-segment depression detected on electrocardiography, which was most prominent in the lateral leads (Fig. S1); and a troponin I level of 6.14 ng per milliliter (reference range, 0 to 0.30). A transthoracic echocardiogram showed severe global left ventricular systolic dysfunction (ejection fraction, 15 to 20%) and normal left ventricular dimensions. Right heart catheterization revealed elevated right- and left-sided filling pressures and a cardiac index of 1.66 liters per minute per square meter of body-surface area as measured by the Fick method. Coronary angiography revealed no obstructive coronary artery disease. An endomyocardial biopsy specimen showed an inflammatory infiltrate predominantly composed of T-cells and macrophages, admixed with eosinophils, B cells, and plasma cells (Fig. 1A and Figs. S2 through S4). She received inotropic support, intravenous diuretics, methylprednisolone (1 g daily for 3 days), and, eventually, guideline-directed medical therapy for heart failure (lisinopril, spironolactone, and metoprolol succinate). Seven days after presentation, her ejection fraction was 60%, and she was discharged home.

Patient 2, a 42-year-old man, presented with dyspnea and chest pain 2 weeks after mRNA-1273 vaccination (second dose). He did not report a viral prodrome, and a PCR test was negative for SARS-CoV-2 (Table S1). He had tachycardia and a fever, and his electrocardiogram showed diffuse ST-segment elevation (Fig. S1). A transthoracic echocardiogram showed global biventricular dysfunction (ejection fraction, 15%), normal ventricular dimensions, and left ventricular hypertrophy. Coronary angiography revealed no coronary artery disease. Cardiogenic shock developed in the patient, and he died 3 days after presentation. An autopsy revealed biventricular myocarditis (Fig. 1B and Figs. S5 and S6). An inflammatory infiltrate admixed with macrophages, T-cells, eosinophils, and B cells was observed, a finding similar to that in Patient 1.

In these two adult cases of histologically con-

firmed, fulminant myocarditis that had developed within 2 weeks after Covid-19 vaccination, a direct causal relationship cannot be definitively established because we did not perform testing for viral genomes or autoantibodies in the tissue specimens. However, no other causes were identified by PCR assay or serologic examination.

Amanda K. Verma, M.D.
Kory J. Lavine, M.D., Ph.D.
Chieh-Yu Lin, M.D., Ph.D.

Washington University School of Medicine
St. Louis, MO
chieh-yu@wustl.edu

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on August 18, 2021, at NEJM.org.

1. Myocarditis and pericarditis following mRNA COVID-19 vaccination. Centers for Disease Control and Prevention, June 2021 (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html).
2. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer–BioNTech COVID-19 vaccination. Pediatrics 2021 June 4 (Epub ahead of print).
3. Larson KF, Ammirati E, Adler ED, et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation 2021 June 16 (Epub ahead of print).
4. Muthukumar A, Narasimhan M, Li Q-Z, et al. In depth evaluation of a case of presumed myocarditis following the second dose of COVID-19 mRNA vaccine. Circulation 2021 June 16 (Epub ahead of print).
5. Rosner CM, Genovese L, Tehrani BN, et al. Myocarditis temporally associated with COVID-19 vaccination. Circulation 2021 June 16 (Epub ahead of print).

DOI: 10.1056/NEJMc2109975

No Correlation betwen Anti-PF4 and Anti–SARS-CoV-2 Antibodies after ChAdOx1 nCoV-19 Vaccination

TO THE EDITOR: Vaccine-induced immune thrombotic thrombocytopenia (VITT), also known as thrombosis with thrombocytopenia syndrome, is a rare but potentially fatal complication of vector-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines.[1-3] The clinical picture and the serologic findings in patients with VITT resemble heparin-induced thrombocytopenia.[1-3] Several groups have reported the presence of platelet factor 4 (PF4)–reactive antibodies in patients with VITT.[1-3] IgG from patients with VITT induces platelet activation and aggregation by cross-linking Fcγ receptor IIA on platelets.[1] PF4 is a tetrameric protein that is released from platelet alpha granules on activation. VITT antibodies bind to the heparin-binding site on PF4.[4] The link between vaccination and the formation of anti-PF4 antibodies is yet to be determined. A proposed mechanism includes cross-reactivity between anti–SARS-CoV-2 and anti-PF4 antibodies.[5] In the current study, we investigated the correlation between anti–PF4–heparin antibodies and anti–SARS-CoV-2 antibodies in vaccinated health care workers (healthy controls) and in vaccinated patients with clinically suspected VITT.

The level of anti–PF4–heparin antibodies was measured with the use of an enzyme-linked immunosorbent assay (ELISA), and the levels of antibodies against various antigenic sites of the SARS-CoV-2 spike protein (spike trimer, receptor-binding domain [RBD], subunit 1 [S1] domain, and subunit 2 [S2] domain) and against nucleocapsid protein were measured with the use of a bead-based assay (Luminex). Antibodies were measured in 101 healthy controls 2 weeks after the first dose of ChAdOx1 nCoV-19 (Oxford–AstraZeneca) had been administered and in 59 patients with clinically suspected VITT between 11 and 22 days after the first dose had been administered. The ability of the sera to activate platelets was tested with the use of a modified heparin-induced platelet aggregation assay. Details of the methods are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

VITT was confirmed in 20 of 59 patients (34%) on the basis of a positive PF4 ELISA and a positive modified heparin-induced platelet aggregation assay (Table S1 in the Supplementary Appendix). The level of anti–PF4–heparin antibodies was higher among the patients with confirmed VITT than among the healthy controls and the patients who did not have VITT (Fig. 1A and Table S1). The 95% confidence intervals for the differences between the groups are presented in Table S2; these confidence intervals were not adjusted for multiplicity and