Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med. DOI: 10.1056/NEJMoa2110737

Supplementary Material

Association of Myocarditis and COVID-19 Vaccination in a Health Care Organization

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Supplementary Methods 1 – The Identification, Adjudication and Abstraction Process

Identification

ICD9 Codes: 422*, ICD9 Code 429.0*, ICD9 Code 398.0*, ICD9 Code 391.2*

Additional confirmation of the diagnostic codes was done by checking the matching of the free text within the diagnosis description field.

Adjudication

Each suspected case was adjudicated through manual review of the patient's electronic medical record. Two cardiologists reviewed each case, the first author (GW), who is a consultant cardiologist, and one of 5 other co-authors who are either consultant cardiologists (SH) or cardiology fellows who are board certified in internal medicine (IR, MW, YA, TG). A case was considered as a true diagnosis if it met the CDC case definition for suspected/probable/confirmed myocarditis (Table S1). In case of disagreement between the reviewers, the senior author (RK), who is a consultant cardiologist, was to review the case and settle the dispute.

Abstraction

Data was collected both from the index hospitalization (defined as the first hospitalization following vaccination where the diagnosis of myocarditis was mentioned) and from subsequent health records. Records inspected included discharge letters from hospital admissions, clinic letters from the community settings, results of imaging studies and laboratory tests, and documentation of medication prescription and procurement. In cases when patients were

admitted to hospitals outside of the CHS network, the hospitals were further approached and requested to forward a copy of the discharge letter.

Table S1 – Case Definition of Myocarditis

Category	Definition
Suspected Case	Dyspnea, palpitations, or chest pain of probable cardiac origin, with either one of the following: A. ECG abnormalities beyond normal variants, not documented previously including: - ST segment/T wave abnormalities - Paroxysmal or sustained atrial or ventricular arrhythmia - Atrioventricular nodal conduction delays or intraventricular conduction defects - Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy B. Focal or diffuse depressed LV function of indeterminate age identified by an imaging study
Probable Case	Meets criteria foe suspected myocarditis, in the absence of other likely cause of symptoms, in addition to one of the following: A. Elevated cardiac enzymes (troponin I, troponin T, or creatine kinase-MB) B. New onset or increased degree of severity of focal or diffuse depressed LV function by imaging C. Abnormal imaging findings indicating myocardial inflammation (CMR with gadolinium, gallium 67 scanning, antimyosin antibody scanning)
Confirmed Case	A. Elevated cardiac enzymes (troponin I, troponin T, or creatine kinase-MB) B. New onset or increased degree of severity of focal or diffuse depressed LV function by imaging C. Abnormal imaging findings indicating myocardial inflammation (CMR with gadolinium, gallium 67 scanning, antimyosin antibody scanning)

Legend: The definition used in the study to adjudicate cases. This definition was originally developed by the CDC to evaluate cardiac events after smallpox vaccine(1).

Abbreviations: ECG, electrocardiogram; LV, left ventricle; CMR, cardiac magnetic resonance imaging.

Table S2 – Criteria for Classification of Myocarditis and Left Ventricular Dysfunction Severity

Category	Definition
Myocarditis Severity	
Low Risk	Typical symptoms of probable cardiac origin: - Chest pain - Supraventricular arrhythmias - Advanced atrioventricular block - Palpitations AND Preserved LV function on imaging study (echocardiography/CMR)
Intermediate Risk	Clinical symptoms as described for mild cases AND Persistent new/worsening abnormalities in LV function not previously known: - Mild or worse LV dysfunction - Persistent regional wall motion abnormalities - Presence of LGE on CMR OR Persistent ECG anomalies OR Frequent non sustained ventricular arrhythmias (without syncope)
Fulminant (High Risk)	- Clinical presentation of decompensated heart failure - Life threatening arrhythmias - Advanced atrioventricular blocks with LV dysfunction - Severe LV dysfunction (New or worsening of known less than severe LV dysfunction) documented on echocardiogram/CMR
Left Ventricular Dysfunction Severity	
Normal	Ejection Fraction greater or equal to 50%
Mild	Ejection Fraction between 50% (exclusive) and 45% (inclusive)
Mild-Moderate	Ejection Fraction between 45% (exclusive) and 40% (inclusive)
Moderate	Ejection Fraction between 40% (exclusive) and 35% (inclusive)
Moderate-Severe	Ejection Fraction between 35% (exclusive) and 30% (inclusive)
Severe	Ejection Fraction under 30% (exclusive)

Legend: Criteria used to classify myocarditis cases by severity. Based on Sinagra et al.(2)

Abbreviations: ECG, electrocardiogram; LGE, late Gadolinium enhancement; LV, left ventricle; CMR, Cardiac Magnetic Resonance imaging;

Table S3 – Presentation, clinical course and follow-up characteristics of the myocarditis cases

Variable	Statistic	Cases with Available Data
Presentation		
Presenting Symptoms and Signs, N (%)		
Chest pain	44 (81.5%)	54
Palpitations	1 (1.9%)	54
Dyspnea	3 (5.4%)	54
Fever	5 (9.3%)	54
Weakness	1 (1.9%)	54
Symptoms of viral infection	5 (9.3%)	54
Pericardial Effusion	10 (20.4%)	49
Vital signs on admission		
Temperature on admission, Mean±SD	37.4±1.0	37
Systolic Blood Pressure, Mean±SD	122.7±16.8	37
Diastolic Blood Pressure, Mean±SD	72.2±11.0	37
Heart Rate, Mean±SD	81.3±17.3	37
Shock, N (%)	1 (2.1%)	47
ECG Findings		
Normal, N (%)	8 (21.1%)	38
Diffuse ST Elevation, N (%)	18 (47.4%)	38
Non-Diffuse ST Elevation, N (%)	2 (5.3%)	38
T wave changes, N (%)	7 (18.4%)	38
Atrial Fibrillation, N (%)	1 (2.6%)	38
Non-sustained Ventricular Tachycardia, N (%)	2 (5.3%)	38
Laboratory Values*		
Elevated Troponin, N (%)	41 (100%)	41
Troponin T, Median (IQR)	680 (275-2075)	41
Elevated Creatine Kinase, N (%)	18 (64.3%)	28
Creatine Kinase, Median (IQR)	487 (230-1193)	28
Elevated C-Reactive Protein, N (%)	38 (97.4%)	39
C-Reactive Protein, Median (IQR)	6.1 (2.0-12.1)	39
Hemoglobin, Median (IQR)	14.5 (13.2-15.4)	38
White Blood Cells, Median (IQR)	8.7 (7.1-12.1)	39

Variable	Statistic	Cases with Available Data
Creatinine, Median (IQR)	0.81 (0.69-0.98)	38
Circulatory Support		
Need for inotropes/vasopressors, N (%)	0 (0%)	48
Need for mechanical circulatory support, N (%)	0 (0%)	48
Clinical Course during Index Hospitalization		
Need for inotropes/vasopressors, N (%)	1 (2.0%)	49
Need for mechanical circulatory support, N (%)	1 (2.0%)	49
Arrhythmias, N (%)	1 (2.0%)	49
Medications at Discharge		
Beta-blockers, N (%)	20 (37.0%) of which 95% new	54
ACE-I/ARB, N (%)	16 (29.6%) of which 75% new	54
NSAIDS, N (%)	12 (22.2%) of which 100% new	54
Colchicine, N (%)	17 (31.5%) of which 100% new	54
Statin, N (%)	5 (9.3%) of which 20% new	54
NOAC, N (%)	1 (1.9%) of which 100% new	54
Prednisone, N (%)	1 (1.9%) of which 100% new	54

* Normal ranges for the laboratory tests: Troponin T, 0-14 ng/L; Creatine Kinase, 20-180 U/L; C-Reactive Protein, 0-0.5 mg/dL; Hemoglobin 13.5-17.5 g/dL (men), 12.0-15.5 g/dL (women); White Blood Cells 4.5-11.0 k/μL; Creatinine 0.67-1.17 mg/dL.

Legend: Characteristics of the myocarditis cases at presentation to the index hospitalization, during the index hospitalization and following discharge. For each variable, the number of cases with data on that row is detailed.

Abbreviations: SD, standard deviation; IQR, inter-quartile range; ACE-I, ace inhibitors; ARB, angiotensin receptor antagonists; NSAIDS, non-steroidal anti-inflammatory drugs; NOAC, novel oral anticoagulants.

Table S4 – Detailed Description of Patients with Unusual Clinical Courses

Event	Details
Fulminant presentation	Male patient in his early 20's, no medical background or treatment, admitted 2 days following the second vaccine dose due to chest pain and fever of 39.0 degrees Celsius. BP On admission ~ 80/45 mmHg HR 110 BPM. Troponin T on admission 275 ng/L, CRP ~ 33 mg/L. Admitted initially to an internal medicine ward but required initiation of vasopressors and transferred to an intensive care unit. Echocardiography reported severe global LV dysfunction (EF=20%). Cardiogenic shock persisted under vasopressors and required mechanical ventilation. Transferred the next day to a tertiary center and put on ECMO. LV function improved gradually and eventually normalized completely. Weaned off ECMO after 16 days and discharged home after a 22 days admission under treatment with aspirin, beta-blockers and ACE-I. LV EF 60% on last echocardiogram pre discharge. No readmissions after a follow up of 68 days. No signs or symptoms of heart failure reported when followed up in the community settings 45 days post discharge.
Mortality	Octogenarian male, medical background of hypertension and ischemic heart disease with a previous MI and PCI over 10 years prior to admission. Known mild-moderate LV dysfunction. Chronic treatment with aspirin, ACE-I, statin and proton pump inhibitors. Admitted 20 days following the 1st vaccine dose due to weakness, no fever on admission, BP ~ 135/65 mmHg, HR ~ 90 BPM. Normal ECG on admission. Troponin T on admission 200 ng/L, CRP ~ 3.5 mg/L. Echocardiogram reported moderate-severe global LV dysfunction (EF=35%). Differential diagnosis was Myocarditis/acute coronary syndrome. Beta blockers and P_2Y_{12} inhibitor were added to his chronic medications. Admitted for four days in stable condition. Was scheduled to undergo an invasive coronary angiogram to rule out acute coronary syndrome but elected to discharge home against medical advice and schedule an elective angiogram. Reported dead at home the day following his discharge. No more details are available for cause of death, and no autopsy was performed.
Readmission	Male patient in his early 50's, medical background of hypertension. Chronic treatment with beta blockers and ACE-I. In 2019 admitted due to pericarditis (pleuritic chest pain, PR depressions on ECG, pericardial effusion on echocardiogram with no evidence of myocardial injury on serial cardiac biomarkers testing), treated with a short course of NSAIDS and discharged. Admitted 6 days following the 1st vaccine dose due to fever and chest pain. BP ~ 130/78 mmHg, HR ~90 BPM. ECG on admission showed PR depressions with no ST segment elevation. Troponin T on admission ~ 100 ng/L, CRP 30.0 mg/L. Echocardiogram demonstrated pericardial effusion with normal LV function. Treated with NSAIDS, Colchicine and Prednisone. Discharged home after a 3 day admission. Admitted 3 weeks post discharge due to pericarditis (pleuritic chest pain, PR depressions on ECG, pericardial effusion on echocardiogram with no evidence of myocardial injury on serial cardiac biomarkers testing), treated with NSAIDS and steroids and discharged 2 days following admission with instructions for gradual tapering of the steroid dosage. 2 subsequent admissions in the following 3 months due to flare ups of pericarditis during steroid tapering. On all admissions normal LV function and normal Troponin T levels. Underwent pericardiocentesis on the second admission with no clues as to the etiology of disease on extensive testing from the pericardial fluid.

* Some of the abovementioned numeric results have been rounded to maintain patient data privacy

Abbreviations: ACE-I, acetylcholine esterase inhibitor; BP, blood pressure; BPM, beats per minute; CRP, C reactive protein; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; HR, heart rate; LV, left ventricular; MI, myocardial infarction; NSAIDS, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention.

Table S5 – Left Ventricular Function at Different Times Relative to the Index Hospitalization

Variable	Admission	Discharge	Follow-up*
N	48	48	5
Qualitative Left Ventricular Function Assessment, N (%)			
Normal	34 (70.8%)	38 (79.2%)	5 (100%)
Mild dysfunction	8 (16.7%)	8 (16.7%)	0 (0%)
Mild-moderate dysfunction	2 (4.2%)	0 (0%)	0 (0%)
Moderate dysfunction	2 (4.2%)	1 (2.1%)	0 (0%)
Moderate-severe dysfunction	1 (2.1%)	1 (2.1%)	0 (0%)
Severe dysfunction	1 (2.1%)	0 (0.0%)	0 (0%)
EF % (Mean±SD)	55.1±8.2	57.5±6.1	--

* Follow-up echocardiography is only reported for patients with LV dysfunction at discharge

Legend: Qualitative left ventricular function and estimated ejection fraction per transthoracic echocardiography performed at admission, discharge and follow-up (median 25 days after discharge) relative to the index hospitalization for myocarditis following vaccination. Follow-up echocardiography was available for 5/10 of the patients discharged with reduced left ventricular function.

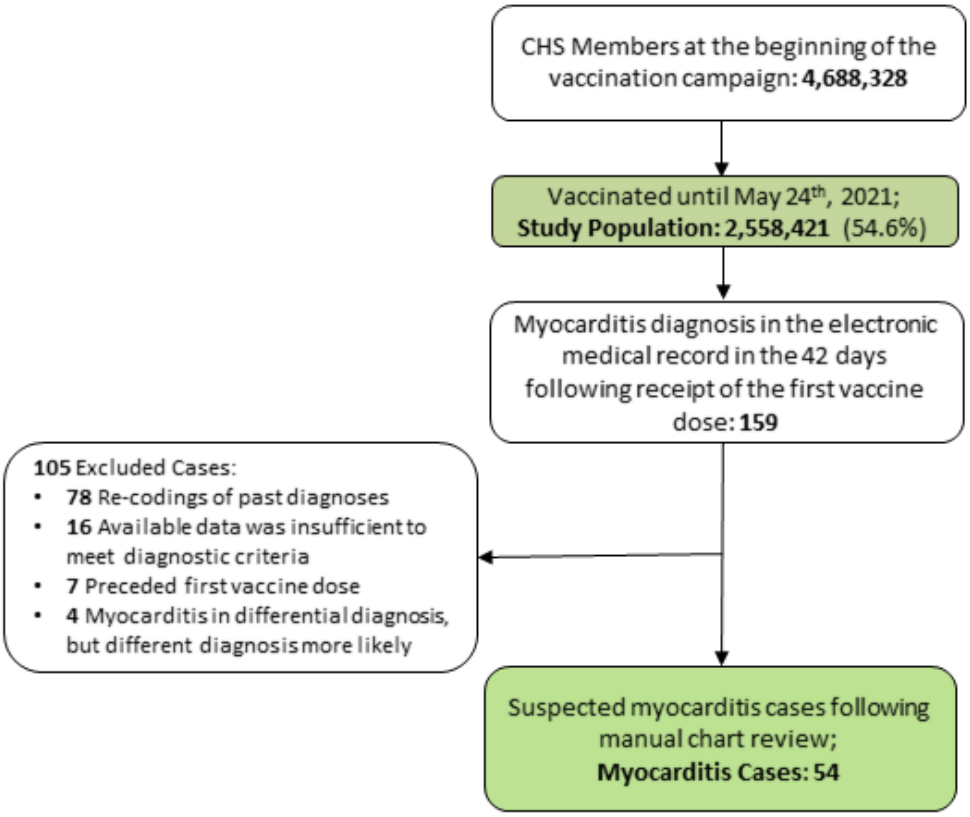
Abbreviations: EF, Ejection Fraction; SD, Standard Deviation; LV, Left Ventricle.

Table S6 – Cardiac MRI data

Variable	Statistic	Cases with Available Data
Ejection fraction, Mean±SD	61.0±5.8%.	15
Reduced Ejection Fraction, N (%)	1 (6.7%)	15
LGE, median, Median (IQR)	5% (1-15%)	11
Any LGE, N (%)	9 (81.8%)	11

Abbreviations: LGE, Late Gadolinium Enhancement MRI; Magnetic Resonance Imaging.

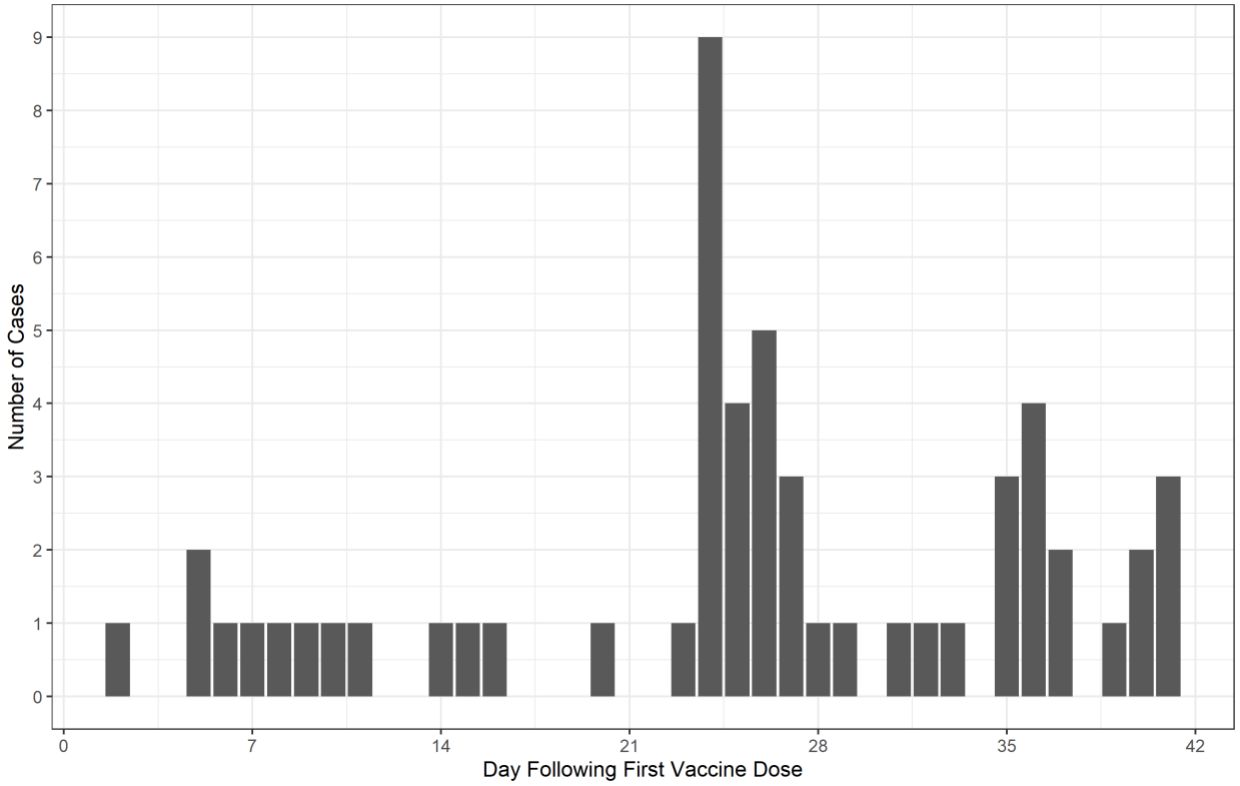
Figure S1 – Population flow chart



Legend: Absolute size of the population at different phases of applying the eligibility criteria, including results of the chart review process.

Abbreviations: CHS, Clalit Health Services.

Figure S2 – Distribution of the days following the first vaccine dose in which myocarditis events occurred



Legend: An "epidemic curve", showing the distribution of days following the first vaccine dose in which myocarditis events occurred.

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1. Centers for Disease Control and Prevention (CDC). Update: cardiac-related events during the civilian smallpox vaccination program--United States, 2003. MMWR Morb Mortal Wkly Rep. 2003 May 30;52(21):492–496.

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