Supplementary Appendix

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

BNT162b2 Vaccination Associated Myocarditis in Israeli Adolescents

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Setting

This study is based on the data of Clalit Health Services. Clalit Health Services is the largest integrated payer-provider health care organization in Israel and provides care for 4.7 million patients (52% of the population). Outpatient care for Clalit Health Services patients is directly provided by the organization, while inpatient care is provided by both in-network hospitals (owned by Clalit Health Services) and out-of-network hospitals. The Clalit Health Services database used for this study have been previously described in detail [1].

Study design and data

This study combined a retrospective cohort study design to evaluate the incidence of myocarditis following the vaccine and a case series to characterize the positive cases. Suspected cases occurring within 42 days of the first dose of the vaccine in adolescents 12-15 years of age were identified by searching for all matching international classification of disease 9 (ICD-9) diagnosis codes (see below) in individuals' electronic medical records, including those recorded for patients with a known history of myocarditis. All adolescents 12-15 who received at least one dose of vaccine between June 2nd 2021 and November 30th 2021 were included. The number of adolescents who left Clalit Health Services during the time of the study is not known so these individuals were treated as not having myocarditis. Electronic medical records for adjudicated cases were reviewed up to February 26th, 2022. The exact definition for myocarditis used in this study is detailed below.

Adjudication

Each suspected case that was identified by electronic medical record review was adjudicated and verified through manual review of the patient's electronic medical record by two cardiologists, the first author (GW), who is a consultant cardiologist, and one of 8 other co-authors who are either consultant cardiologists (SH, YTB, MY, YA, AS, NSP) or cardiology fellows who are board certified in internal medicine (IR, TG). A case was considered as a true diagnosis if it met the CDC case definition for suspected/probable/confirmed myocarditis (see below). 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. The median number of confirmed cases per adjudicator was 1 (IQR 1-1)

Abstraction

The data was collected from the index hospitalization (defined as the first hospitalization following vaccination where the diagnosis of myocarditis was mentioned) and from subsequent health records, including discharge letters from hospital admissions, clinic letters from community practices, 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 Clalit Health Services network, the hospitals were approached and a copy of the discharge letter was requested.

Statistical Analysis

To estimate the incidence, individuals were followed until the earliest of outcome event, 42 days post-vaccination, death from unrelated causes (in the latter two cases they were considered censored). The cumulative incidence of myocarditis was

estimated using the Kaplan-Meyer estimator 42 days after the first vaccine dose, stratified by age and sex. Categorical variables were summarized using counts (%), and continuous variables using the mean (±standard deviation) if their distribution appeared normal, or the median (interquartile range) otherwise. Outcome variables are presented noting the number of patients who had data in their chart regarding the specific variable.

Ethics

This study was approved by the Clalit Health Services institutional review board. The study was exempt from informed consent. The First and Senior authors (GW, RK) vouch for the integrity of the data.

Definition of Myocarditis used for Initial Search

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.
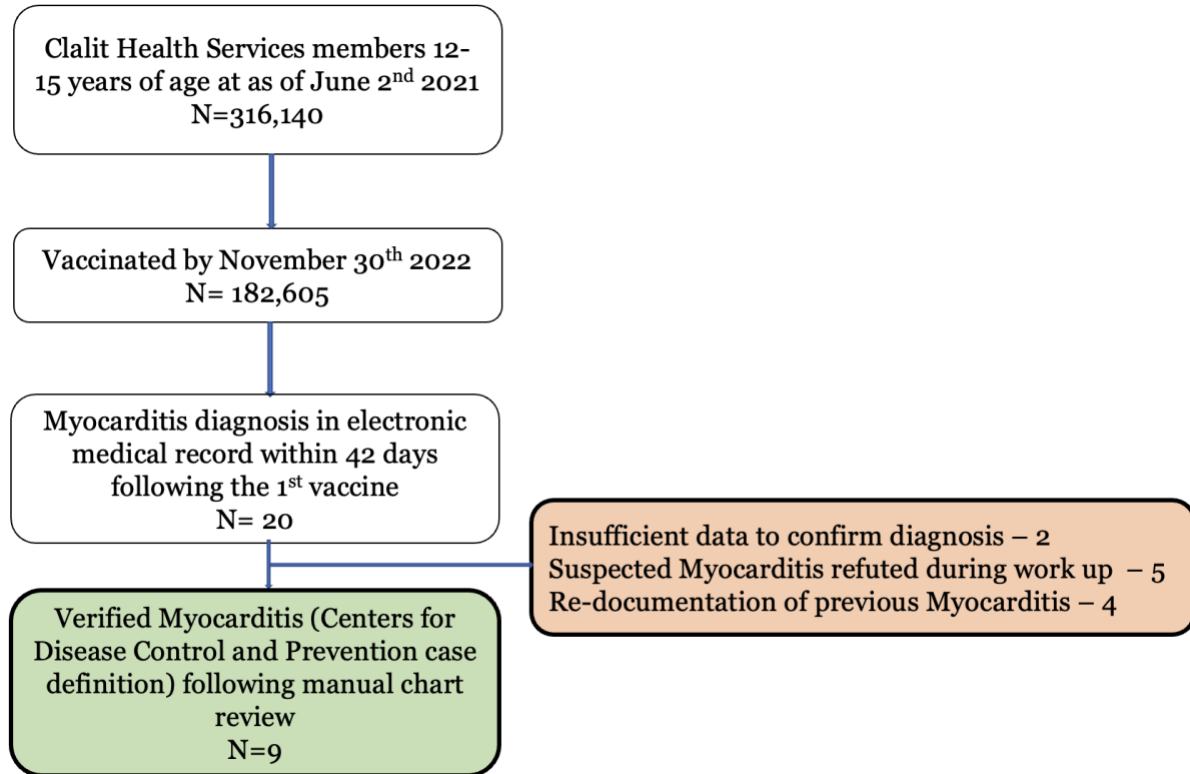
CDC Case Definition of Vaccine associated Myocarditis

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(2).
Abbreviations: ECG, electrocardiogram; LV, left ventricle; CMR, cardiac magnetic resonance imaging.

Supplementary figures:

Figure S1 – Study flow chart

Clalit Health Services members 12-15 years of age at as of June 2nd 2021
N=316,140

Vaccinated by November 30th 2022
N= 182,605

Myocarditis diagnosis in electronic medical record within 42 days following the 1st vaccine
N= 20

Insufficient data to confirm diagnosis – 2
Suspected Myocarditis refuted during work up – 5
Re-documentation of previous Myocarditis – 4

Verified Myocarditis (Centers for Disease Control and Prevention case definition) following manual chart review
N=9

Supplementary tables:

Table S1 – Baseline characteristics of the verified myocarditis cases

	`Verified cases of myocarditis following booster vaccination N=9	No myocarditis following booster vaccination N-182,596
Age (years; median (IQR))	14 (13-14)	13(12-14)
Sex (%)		
Female	1 (11.1%)	90,385(49.5%)
Male	8 (88.9%)	92,211(50.5%)
Population Sector (%)		
General Jewish	9 (100%)	121,609(66.6%)
Arab	0 (0%)	50,944(27.9%)
Ultra-Orthodox Jewish	0 (0%)	10,1043(5.5%)
Socioeconomic Status (%)		
Low	4 (44.5%)	102,802(56.3%)
Medium	5 (55.5%)	75,960(41.6%)
High	0 (0%)	3,834(2.1%)
Background Diseases (%)		
Attention deficit hyperactive disorder	1 (11.1%)	
Benign ethnic neutropenia	1 (11.1%)	
Previous Myocarditis	0 (0%)	
Previous Pericarditis	0 (0%)	
Known LV Dysfunction	0 (0%)	
Any Background Disease	2 (22.2%)	
Baseline medication Use (%)		
Methylphenidate	1 (11.1%)	
Any Baseline Medications	1 (11.1%)	

Legend: baseline demographics characteristics, background diseases and baseline drug use of the verified myocarditis cases. Socioeconomic status is based on Clalit Health Services internal registries using the patient's primary care clinic location.

Abbreviations: IQR, interquartile range.

Table S2 – Incidence of myocarditis 42 days following receipt of the first vaccine dose, stratified by age, sex and disease severity

Population	N	Number of cases	Incidence per 100,000 (95% CI)
All Cases			
Entire Population	182,605	9	4.93 (1.7 – 8.15)
Males	92,200	8	8.68 (2.66-14.69)
Females	90,405	1	1.11 (0-3.27)
Age 12 years	46,953	1	2.13 (0-6.3)
Age 13 years	45,765	3	6.56 (0-13.97)
Age 14 years	45,107	3	6.65 (0-14.17)
Age 15 years	44,780	2	4.47(0-10.66)

Legend: Incidence proportion per 100,000 individuals was estimated using the Kaplan-Meier estimator. Disease severity was defined as detailed in the text. CI: Confidence Interval.

Total Population, Ages 12-15: 316,140

Table S3 – Presentation clinical course during the index admission

Variable	Statistic	Number of cases with available data
Presentation		
Presenting Symptoms and Signs		
Chest pain (%)	9/9(100.0%)	9
Palpitations (%)	1/9(11.1%)	9
Dyspnea (%)	2/9(22.2%)	9
Fever (%)	7/9(77.7%)	9
Nausea and vomiting (%)	3/9(33.3%)	9
Myalgia (%)	1/9(11.1%)	9
Pleuritic pain (%)	1/9(11.1%)	9
Symptoms of viral infection (%)	0/9)0%)	9
Pericardial Effusion (%)	4/9(44.4%)	9
Vital signs on admission		
Temperature on admission (Mean±SD)	37.8±0.8	9
Systolic Blood Pressure (Mean±SD)	114.5±14.2	9
Diastolic Blood Pressure (Mean±SD)	66.2±11.1	9
Heart Rate (Mean±SD)	90.8±13.1	9
Shock (%)	0/9 (0%)	9
ECG Findings		
Normal (%)	3/9(33.3%)	9
Diffuse ST Elevation (%)	2/9(22.2%)	9
Non-Diffuse ST Elevation (%)	3/9(33.3%)	9
ST segment depression (%)	1/9(11.1%)	9
T wave changes (%)	1/9(11.1%)	9
Laboratory Values		
Troponin T (Median (IQR))	820(716-940)	7
Troponin I (Median (IQR))	9487(4631-14613)	2
Creatine Kinase (Median (IQR))	602 (398-792)	6
C-Reactive Protein (Median (IQR))	8.5(1.6-11.0)	9
Hemoglobin (Median (IQR))	13.4 (12.4-14.2)	8
White Blood Cells (Median (IQR))	6.8 (5.2-8.0)	7
Erythrocyte sedimentation rate (Median (IQR))	13 (13-13-13)	2
Circulatory Support		
Need for inotropes/vasopressors (%)	0/9 (0%)	9
Need for mechanical circulatory support (%)	0/9 (0%)	9

Variable	Statistic	Number of cases with available data
Clinical Course during Index Hospitalization		
Need for inotropes/vasopressors (%)	0/9 (0%)	9
Need for mechanical circulatory support (%)	0/9 (0%)	9
Arrhythmias (%)	0/9 (0%)	9
Medications at Discharge		
NSAIDS (%)	6/9 (66.6%)	9
Colchicine (%)	1/9 (11.1%)	9
Admission length		
Length of stay (days) (Median (IQR)	3 (2-4)	9

Legend: Characteristics of the verified 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.   Length of stay (days) (Median (IQR))

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

Table S4 – Echocardiographic assessment during the index admission

Variable		Number of cases with available data
Qualitative Left Ventricular Function Assessment (%)		9
Normal	8/9(88.9%)	
Mild dysfunction	1/9(11.1%)	
Ejection Fraction (Mean±SD)	60.0±5.0 (N=5)	5
Pericardial effusion (%)	4/9(44.4%)	9
Minimal (%)	1/9(11.1%)	
Small (%)	2/9(22.1%)	
Unspecified (%)	1/9(11.1%)	

Legend: Qualitative left ventricular function and estimated ejection fraction per trans-thoracic echocardiography performed at admission and discharge from the index hospitalization for myocarditis following vaccination.

Abbreviations: SD, Standard Deviation

* Resolution of pericardial effusion in 2 cases with available TTE on follow up (in both cases the effusion was small to begin with).

Supplementary references:

[1] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 Apr 15;384(15):1412–1423.

[2]. 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.