Supplementary Appendix

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

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Supplementary Materials

CONTENTS

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Methods

Detection of SARS-2 antibodies and PCR. The levels of specific anti-SARS –CoV-2 spike protein (S) receptor binding domain (RBD) IgG were assessed in serum specimens using the Architect SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics, Chicago, USA), according to the manufacturer's specifications.

SARS-CoV-2 RNA was detected using multiplex real-time RT-PCR for the simultaneous detection of the SARS-CoV-2–specific E gene and a human ERV3 gene as an internal control. Primers and probes were purchased from Integrated DNA Technologies. Real-time RT-PCR was performed using the TaqPath qPCR Master Mix on the QuantStudio 5 Real-Time PCR Instrument (Applied Biosystems Inc.).

Clinical characteristics of patients diagnosed with myocarditis. All relevant clinical material related to these cases was forwarded to one of four board-certified cardiologists. To unify definitions and classifications the cardiologists and a board-certified rheumatologist met before initiating work and a uniform inclusion criteria and classifications were written. A predesigned table including the key clinical features and classifications was generated and filled. Disputed or questionable cases were marked by the cardiologist in charge of the case and discussed by a committee including D.M. (a rheumatologist), T.H., N.L., R.A, O.A., (cardiologists), to reach

consensus. Classifications were based on the Brighton criteria (see main manuscript and appendix) and smallpox criteria (table S1).

Comparison of observed-to-expected ratio based on historical data. Data for the Israel's National Hospitalization Discharge Database (NHDD) are uploaded periodically by every medical facility and are usually complete and validated within 6–12 months. Finalized data for late 2020 and 2021 were thus not available at the time of the analysis. For the purpose of this study, we therefore relied on data received directly from all hospitalizations on subjects aged ≥16 years where myocarditis (ICD-9 codes 422.0-9x and 429.0x) was the primary reason for admission during two reference periods: 2017–2019, before COVID-19 was identified in Israel, and 2020, when there was COVID-19 circulation.

The expected incidence of myocarditis in vaccinated subjects was computed based on 21- and 30-day averages for the first and second vaccine doses, respectively, and compared to both reference periods (2017–2019; 2020), since there was no significant seasonal difference in myocarditis hospitalizations (Table S2). The results were very similar for both reference periods, and therefore the data shown in the manuscript refers to the expected incidence based on the more stable (with respect to completeness and data validation) 2017–2019 period. The expected number of myocarditis cases was estimated based on this historical incidence rate, weighted by the number of vaccinated individuals. The observed number of myocarditis cases included all cases that occurred in proximity to vaccination (21 and 30 days following the first and the second vaccine doses, respectively), regardless of the diagnosis categorization (N=151). The rationale for this decision was that myocarditis was ascertained by a team of clinicians during active

surveillance, while this was not the case for historical cases; therefore, we have decided not to restrict the analysis to the most certain cases.

Rate-Ratio (RR) analysis. Based on findings from the SIR analyses, a cohort analysis was conducted focusing only on recipients of the second dose of COVID-19 vaccine. Only cases categorized as probable (suspected) or definitive (certified) were included in this analysis to limit the potential for misclassification of myocarditis. To cover the period from January 11, 2021, the day on which the second doses of vaccine were first administered in Israel, to May 31, 2021, a series of 141 cohorts of vaccinated individuals was created, excluding people with known myocarditis, each starting on 1 day within this time window. These 141 cohorts were followed up for 30 days each, to determine whether there was a diagnosis of myocarditis. The comparison group consisted of nonvaccinated individuals on January 11, excluding people diagnosed with myocarditis. Since data for the comparison group were mainly aggregated, we have examined these individuals throughout the total study period: January 11 up to June 30, which was chosen because it includes the 30-day follow-up window following administration of the second vaccine dose on May 31. In this comparison group, each individual contributed one person-day at risk for each passing day, as long as they remained unvaccinated and were not diagnosed with myocarditis. While computing incidence rates, we have summed up the total number of myocarditis cases and person days at risk in the vaccinated individuals across the 141 cohorts. In the nonvaccinated group, all myocarditis cases and person days at risk throughout the follow up period were used. (Fig. S1). Analyses were repeated using the smallpox classification.

Results

During the surveillance period, 5,442,696 people of different age groups received the first vaccine dose, and 5,125,635 people received two doses. The peak occurrence of myocarditis diagnoses was in February and March 2021 (Fig. S2).

Clinical characteristics of patients diagnosed with myocarditis. The diagnosis was based on symptoms (mainly chest pain or dyspnea) that typically appeared 1–4 days following vaccination, electrocardiographic abnormalities, elevated troponin T, imaging by an echocardiogram and/or cardiac magnetic resonance imaging (cMRI) and/or endomyocardial biopsy and lack of evidence for coronary heart disease.

Among 304 cases of myocarditis reported from 12/2020–31/05/2021, 21 had alternative diagnoses, and 283 were classified as definitive, probable, possible, or myocarditis with insufficient data based on the Brighton criteria. 142 cases, including 70 with perimyocarditis, were identified in temporal proximity to vaccinations. 136/142 cases of definitive or probable myocarditis following vaccination presented with chest pain (95%), fever (46.7%), dyspnea (12.5%), elevated troponin I or T (100%, Normal <53, range 103–15,036 for most,), elevated C-reactive protein (86.7%), and ECG changes (69%). The tropinin t level was >250,000 in one patient. Additional laboratory findings included mild lymphocytopenia, and, if examined, modest NT Pro-BNP elevation. Most cases 129/136 (94.8%) were uneventful, while the clinical course was moderate to severe in 7/136 (5.2%).

Ejection fraction (EF) was normal or mildly reduced in most patients and severely reduced in 4 patients. cMRI, performed in 48 (35.2%) patients, disclosed mild-to-moderate subepicardial and mid-myocardial late gadolinium enhancement (LGE) more significantly affecting the lateral and inferior LV segments. Endomyocardial biopsy, performed in two patients with myocarditis, revealed foci of endo-interstitial edema and neutrophils, and mononuclear cell infiltrates (monocytes/macrophages and lymphocytes) with no giant cells.

None of the patients had symptoms or PCR consistent with concomitant COVID-19, and 35/39 (90%) who were tested were negative for anti-nucleocapsid (anti-N) serology, reducing the likelihood of recent prior COVID-19. Anti-spike protein (anti-S) serology tests were positive in 62/62 patients examined (100%), consistent with an immune response due to COVID-19 vaccination.

Most patients (129/136) experienced significant clinical improvement, and the average length of hospitalization was 3–4 days, with 1 patient requiring readmission after discharge. Most of these patients were treated with nonsteroidal anti-inflammatory medication (NSAIDS), with or without colchicine for presumed pericardial inflammation.

Overall, 7/136 (4.9%) patients had a significant clinical course, with 1/136 (0.7%) fatality. In the seven patients with a complicated disease course there were one or more of the following findings: greater than moderate left ventricular dysfunction, ventricular arrhythmia, clinical heart failure, death. Some were reported to respond very well to corticosteroids. One 22-year-old patient with fulminant myocarditis, including troponin T levels >250,000, died within 24 hours of diagnosis.

In addition to the Brighton criteria presented in the manuscript, the cases were also classified according to smallpox criteria (Supplementary Table S1 and appendix), which have been used in the past for myocarditis associated with smallpox vaccines.[1-3] According to these criteria there were 106/142 confirmed or probable cases, (2/142) cases of suspected myocarditis, and 34/142 cases with insufficient data . The last two categories were not included in myocarditis analyses to increase the probability that only accurate diagnoses were considered.

Incidence rates in individuals who received two vaccine doses vs unvaccinated individuals. Rate ratio (RR). Results of the RR analysis based on the smallpox classification of myocarditis (definitive and probable cases only) were similar to those using the Brighton classification with respect to males in younger age groups: 16–19y RR=9.54 (95%CI 4.49 to 20.28), 20–24y RR=6.79 (95%CI 3.23 to 14.27), 25–29y RR=2.98 (95%CI 1.47 to 6.03).

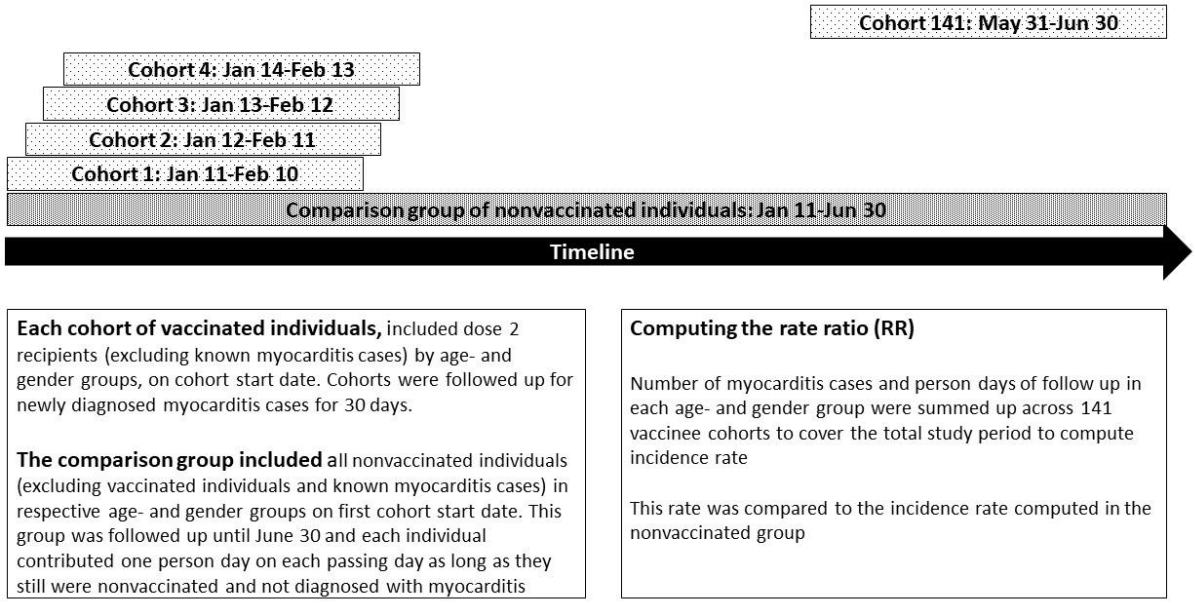
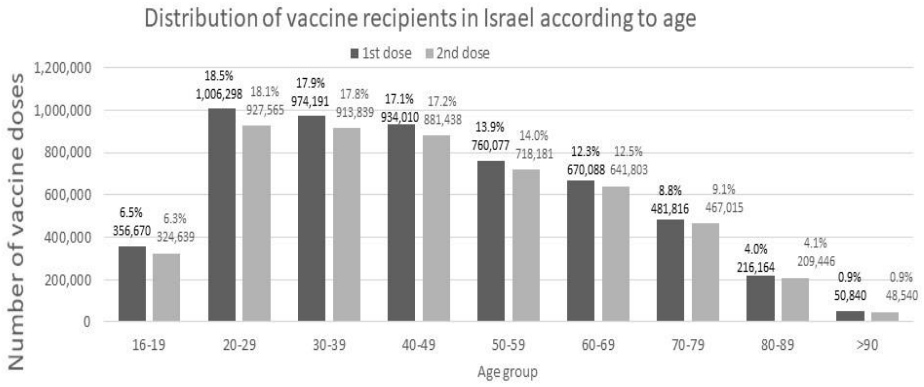


Figure S1. Rate ratio computation based on a series of vaccinated cohorts and a comparison group.



AgeGroup	16-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90<
Vaccine coverage by age group 1st dose	61.1%	77.4%	81.4%	85.0%	89.4%	90.4%	98.2%	95.8%	98.7%
Vaccine coverage by age group 2nd dose	55.6%	71.3%	76.3%	80.2%	84.5%	86.5%	95.2%	92.9%	94.3%

Figure S2. Mevorach et al.

Figure S2. Distribution of vaccine recipients according to age and dose by May 31, 2021. Upper figure. No. and percentage of vaccinated individuals by age group. Lower table. Percentage of vaccinated individuals by age group.

Supplementary Table S1. Classification of reported myocarditis cases

Smallpox classification (1=confirmed; 2=probable; 3=suspected; 4= insufficient data; 5=ruled out)							
		1	**2**	**3**	**4**	**5**	**Total**
Vaccinated	Myocarditis within 21 days following the 1st dose and 30 days following the 2nd dose	2	105	1	34	9	151
	Myocarditis more than 21 days following the 1st dose and 30 days following the 2nd dose	1	30	0	9	5	45
Not vaccinated		3	79	3	16	7	108
Total		6	214	4	59	21	304

Supplementary Table S2. Number of hospitalizations due to myocarditis[1] as the main hospitalization cause by gender and by month and year, 2017-2020

Month/year	**Males**				**Females**			
	2017	2018	2019	2020	2017	2018	2019	2020
January	23	29	28	32	7	7	5	14
February	23	23	29	32	6	4	7	6
March	20	35	31	32	7	7	3	4
April	23	30	32	14	1	6	8	6
May	24	31	26	13	4	3	8	4
June	28	24	32	17	4	6	3	3
July	24	15	30	17	2	7	5	5
August	31	20	22	32	7	4	7	7
September	20	21	23	16	4	4	4	3
October	17	15	29	17	4	3	7	3
November	25	18	29	20	7	4	5	8
December	37	21	24	22	6	7	10	3
Total	**295**	**282**	**335**	**264**	**59**	**62**	**72**	**66**
30-day average[2]	***24.2***	***23.2***	***27.5***	***21.7***	***4.8***	***5.1***	***5.9***	***5.4***

[1] ICD-9 codes for myocarditis include 422.0-9x and 429.0x

[2] A 30d average was computed by dividing the annual number of hospitalizations in each calendric year by 365 and multiplying the result by 30

Supplementary Table S3. Characteristics of patients presented with definitive or probable myocarditis or myopericarditis following Pfizer-Biontec BNT162b2 vaccination for COVID-19.

Chest pain	Dyspnea	Palpi-tations	Fever	ECG changes	Elevated Troponin I or T	Elevated C-reactive protein (CRP)	COVID-19 (PCR)	Anti-spike protein	Anti-nucleo-capsid
129/136 (95%)	17/136 (12.5%)	6/136 (4.4%)	63/136 (46.7%)	93/136 (68%)	136/136 (100%)	118/136 (86.7%)	Negative 136/136 (100%)	Positive 62/62 (100%)	Negative in 35/39 (90%)

Supplementary Table S4. Sensitivity analysis - examining the potential for over-reporting of myocarditis/perimyocarditis[1] needed to produce the actual results – males only, vaccine dose 2 only (N=110)

Age group	Vaccine dose 2 – actual results				Sensitivity analysis			
	a. # Observed	b. # expected by 2017-2019 reference[a]	# Vaccinated	SIR (95%CI)	c. Minimal # needed for a significant SIR	d. SIR (95%CI) expected if number observed was equal to "c"	Extra reports needed for the actual results a/(c-1)[b]	Assumed over-reporting in %
16–19	32	2.35	199,115	13.60 (9.30–19.20)9.30–19.20)	7	2.98 (1.19-6.13)	X5.3	430%
20–24	26	3.05	239,396	8.53 (5.57–12.50)	8	2.63 (1.13–5.17)	X3.7	270%
25–29	20	2.87	228,988	6.96 (4.25–10.75)	8	2.78 (1.20–5.49)	X2.9	190%
30+	32	11.04	1,839,711	2.90 (1.98–4.09)	19	1.72 (1.04–2.69)	X1.8	80%

[a]Based on a 30-day average incidence in 2017-2019

[b]Extra reports needed for the actual results were computed by dividing the number of observed cases by the minimal number of cases needed for a significant result minus 1 (assuming incidence which is similar to the expected incidence)

Supplementary Table S5. Bradford-Hill criteria of causality with respect to the association observed between receipt of the second dose of the Pfizer-BioNTech vaccine mRNA COVID-19 vaccine and idiopathic myocarditis

#	Criteria	Status	Comment
1	Strength of association	V	Association measures for the risk of myocarditis in younger males during the first week following administration of vaccine dose 2 were strong
2	Consistency	V	Similar observations albeit weaker reported from other countries[1-3]. In addition, we have used three different approaches to assess the association and all yielded similar results
3	Specificity	X	A weak criterion; the vaccine causes other adverse effects and myocarditis has many other etiologies
4	Temporality	V	Very strong; most cases occurred within one week of vaccine dose 2 administration. Additionally, the incidence of myocarditis declined markedly as the number of people newly vaccinated declined.
5	Biological gradient	V/X	Most cases occurred following vaccine dose 2 but under the current setting (vaccination campaign), this criterion may be less relevant
6	Plausibility	V	Adverse effects following vaccination are well-known phenomena; myocarditis following vaccination was reported for other vaccines
7	Coherence	V	Some biological mechanisms were suggested to explain the observed association; in addition, special effort was put in order to rule out other potential causes for myocarditis
8	Experiment	X	Not observed in producer's RCTs, but the numbers in the RCT setting were much smaller
9	Analogy	V/X	Other vaccines (e.g., smallpox) were previously reported to be associated with myocarditis as an adverse effect, but there is no experience with previous mRNA vaccines

V=criterion applies; X= criterion does not apply; X/V=uncertain

Appendix: Myocarditis classifications

Case definition by the recommended classifications based on Brighton Collaboration

Myocarditis Case Definition (Pandemic Emergency Response Process)[4]

Myocarditis and perimyocarditis are defined as a spectrum of disease caused by inflammation of the myocardium (myocarditis) or myocardium and pericardium (perimyocarditis). Symptoms and signs may be consistent with myocarditis, pericarditis, or both. For surveillance reporting, patients with myocarditis or perimyocarditis are reported. These categories are intended for surveillance purposes.

Definitive case (Level 1):

1. Histopathologic examination showing myocardial inflammation.

OR

2. Elevated troponin AND EITHER
    a. cMRI with myocarditis specific changes

    OR

    b. Abnormal echocardiography. Evidence of focal or diffuse depressed left ventricle (LV) function identified by an imaging study, i.e. echocardiography, or that is documented to be of new onset or increased degree of severity. In the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow-up studies, these findings resolve, improve, or worsen.

Probable case (Level 2):

1. Clinical symptoms as for the possible case

AND

2. Any 1 of the following 3 findings
    a. Elevated troponin I or T, or CPK MB

    OR

    b. Echocardiogram abnormalities

    OR

c. EKG changes

Possible case (Level 3):

1. One of the following symptoms: dyspnea, or palpitations, or chest pain or pressure, or diaphoresis, or sudden death in a patient

OR

2. Two of the following symptoms: fatigue, gastrointestinal, dizziness or syncope, edema, or cough.

AND

3. Supportive laboratory biomarkers: elevated CRP, or elevated D-dimer, or elevated ESR

AND

4. Nonspecific EKG abnormalities: St-T or T waves changes, or premature complexes.

AND

5. The absence of evidence of any other likely cause of symptoms or findings

Insufficient evidence (Level 4) to meet level 1, 2, 3 classifications in a reported myocarditis case

Not myocarditis (Level 5)

Case definition by the recommended classifications based on myocarditis associated with smallpox vaccination[5-7] Myocarditis and perimyocarditis are defined as a spectrum of disease caused by inflammation of the myocardium (myocarditis) or myocardium and pericardium (perimyocarditis). Symptoms and signs may be consistent with myocarditis, pericarditis, or both. For surveillance reporting, patients with myocarditis or perimyocarditis are reported. These categories are intended for surveillance purposes and not for use in individual diagnoses or treatment decisions, and are based on the recommended classifications used for myocarditis associated with smallpox vaccination.[5]

Suspected case of acute myocarditis is defined by the following criteria:

1. Presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a patient.

AND

2. Any one of the following
    a. Electrocardiogram (ECG) abnormalities beyond normal variants, not documented previously, including ST-segment or T-wave abnormalities, paroxysmal or sustained atrial or ventricular arrhythmias, AV nodal conduction delays, or intraventricular conduction defects, or continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy.

    OR

    b. Evidence of focal or diffuse depressed left-ventricular (LV) function of indeterminate age identified by an imaging study (e.g., echocardiography or MRI).

Probable case of acute myocarditis/perimyocarditis: meets the criteria for a suspected case without an alternative cause and has **one of the following**:

1. Elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred);

OR

2. Evidence of focal or diffuse depressed left ventricle (LV) function identified by an imaging study, i.e. echocardiography, or that is documented to be of new onset or increased degree of severity. In the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow-up studies, these findings resolve, improve, or worsen.

OR

3. Abnormal result of cardiac MRI with gadolinium, indicating myocardial inflammation.

Confirmed case of acute myocarditis/perimyocarditis: Histopathologic evidence of myocardial inflammation is found at endomyocardial biopsy or autopsy.

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