Supplementary Appendix

Supplement to: Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 vaccination in Israeli adolescents. N Engl J Med. DOI: 10.1056/NEJMc2116999

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

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Supplementary Materials CONTENTS

Methods

Active surveillance. Cases of suspected myocarditis are almost always hospitalized in Israel, and therefore active surveillance requesting all hospitals to report cases of myocarditis weekly, regardless of vaccination status, should identify virtually all cases of myocarditis during the period of active surveillance. We reviewed data regarding presumptive cases of myocarditis in the age group of ≥12 − <16y (i.e., 12-15) retrospectively from medical records, including clinical and laboratory data and discharge summaries starting June 2, 2021 (the first day of vaccination of this age group) through October 20, 2021 (to allow for a 30d follow up in those vaccinated on September 20, 2021). All records were reviewed by a board-certified cardiologist and a board-certified rheumatologist for verification of the diagnosis of myocarditis. Reviewers were not masked to the vaccination status of patients. Diagnostic criteria for myocarditis were adapted from the case definition and classification of the Brighton Collaboration Myocarditis Case Definition,[1] similarly to our previous report.[2] The study was conducted as part of an ongoing clinical surveillance for COVID-19 vaccine-related side effects as required by national guidelines; thus, it received an IRB waiver. Pfizer had no role in data collection, analysis, or reporting of data in this paper.

Descriptive frequencies, percent, means, and standard deviations were used to characterize cases by age, gender, time elapsed since vaccination, hospital length-of-stay, and clinical outcome.

Results

Between June 2 and September 20, 2021, 404,407 adolescents (195,579 males) received the first vaccine dose and 326,463 (157,153 males) received two doses. A total of 18 cases with ICD-9 codes for myocarditis (ICD-9 422.0-9x and 429.0x) were reported to the Ministry of Health. Following review and using the Brighton classification of myocarditis,[1] two cases were excluded due to reasonable alternative diagnoses. Out of the rest 16 cases, 13 cases were diagnosed following the follow-up period of vaccination: 1 case was diagnosed within 21 days following the first vaccine dose, and 12 within the first week following the second vaccine dose (Fig. 1). Two more cases were diagnosed 46 and 70 days after the second vaccination, respectively, and therefore were not considered related to the vaccine and one additional case of myocarditis occurred in an unvaccinated adolescent.

Each clinician reviewed all cases independently, followed by a joint discussion to compare definitions for each case. No disagreements were noted.

The great majority of cases following vaccination, 12/13, were reported in males. Demographic and clinical characteristics of myocarditis patients are summarized in Tables S1 and S2. The diagnosis was based on symptoms, mainly chest pain that typically appeared 1–4 days following the second vaccination, electrocardiographic abnormalities in some patients, and documentation of elevated high-sensitivity cardiac troponin in all patients. Echocardiography was performed in all patients and was normal in 11/13; cardiac MRI during hospitalization was performed in one, confirming the diagnosis of myocarditis. Of the 13 patients who developed

myocarditis in proximity to vaccination based on the Brighton diagnosis criteria, all were classified as definitive or probable.

Ejection fraction (EF) was normal or mildly reduced in all patients. In those with mildly reduced left ventricular function (n=2), early normalization was noted during the hospitalization. None of the patients had symptoms or PCR consistent with concomitant COVID-19 and a viral panel performed in 9/13 and was negative in all cases. No attempt to isolate heart viruses was made.

The average hospitalization stay was 3.1 days (range 1−6 days), with no readmissions after discharge. 10/13 patients were treated with nonsteroidal anti-inflammatory medication and one with corticosteroids. None had a significant clinical course, and no fatalities were documented. Ethnicity, age, and gender, as well as gender of the broader population affected by myocarditis and comments on the representativeness of patients are given in Table S2. Table S3 refers to the representativeness of study participants.

Discussion

The pattern observed, mainly following the second vaccination in males, suggests causality; therefore, 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 in adolescents were established (Table S4). The risk compared to our previous study for ages 16−30[2] was lower. The possible explanation for lower risk at ages 12−15 compared to 16−19 may be related to male sexual maturity and a general decrease in occurrence of myocarditis at this age,[3] and thus may indicate expected lower incidence in children <12 years.

Two additional cases diagnosed 46 and 70 days after the second vaccination, respectively, were not considered related to the vaccine. Due to the rarity of myocarditis in this age group, this may suggest that the follow up period should be extended, however, it may also represent background morbidity, which was 1.62/100,000 in males and 0.80/100,000 in females in this age group for the years 2017−2019, based on historical hospitalization data.

Affected patients were advised to reduce sports for six months from the event and return to sports only after a follow-up visit with a cardiologist that includes echocardiogram and MRI. All patients were advised not to get a booster mRNA vaccine (from any company), but boosters of non-mRNA vaccines were permitted. The long-term follow-up plan includes at least 1 year with four echocardiograms and two MRI studies in addition to clinical and laboratory follow-up.

References

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Supplementary Table S1. Age, gender, and other sociodemographic information of 13 Adolescents with myocarditis after vaccination: No./total no. (%).

Age
12 years 1/13, (8.3%)
13 years 5/13 (38.4%)
14 years 4/13 (7%γ30)
15 years 3/13 (23.0%)

Gender
Males: 12/13 (92%); females 1/13 (8%)

Ethnicity
Jews 12/13, (92%)
Moslems 1/13, (8%)
Sephardic Jews 7/12 (58%)
Ashkenazi Jews 5/12, (42%)

Background diseases

Healthy 11/13 (84.6%)

Congenital neutropenia 1/13 (7.7%)

Schizophrenia 1/13 (7.7%)

Supplementary Table S2. Presentation and clinical course of 13 adolescents with myocarditis after vaccination: No./total no. (%).

Presenting symptoms and signs
Chest pain 13/13, (100)
Palpitations 2/13 (15.4)
Dyspnea 4/13 (30.8)
Fever 4/13 (30.8)

Laboratory values
Elevated high-sensitive troponin – 13/13 (100), range 207−30,000, N up to 17/53
Elevated C-reactive protein –12/13 (92), average 4.4 mg%, range 0.88−11.0, N up to 0.5

Vital signs on admission. Plus–minus values are means ±SD.

Blood pressure — mm Hg
Systolic 110±12.5
Diastolic 66±8.2
Heart rate 81.3±17.3 beats per min
Shock — 0/13 (0%)

Electrocardiographic findings — no./total no. (%)
Normal 7/13 (53.8)
ST-segment elevation 5/13 (38.5)
Diffuse 2/13 (15.4)
Nondiffuse 3/13 (23.1)
T-wave change 2/13 (15.4)
Atrial fibrillation 0/13 (0)
Unsustained ventricular tachycardia 0/13 (0)

Echocardiography
Pericardial effusion 3/13 (23.1)
Abnormal LV function 2/13 (15.4)

Clinical course during index hospitalization
Need for inotropes or vasopressors 0/13 (0)
Need for mechanical circulatory support 0/13 (0)
Arrhythmias 0/13 (0)
Length of stay 3.1 days (range 1−6)

Supplementary Table S3. 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 in adolescents

#	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 (Figure 1).
2	Consistency	**v**	Similar for ages observations for ages 12-17, albeit weaker reported from other countries.[2,4]
3	Specificity	**x**	A weaker criterion; the vaccine causes other adverse effects and myocarditis has many other aetiologies
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**	Most cases occurred following vaccine dose 2
6	Plausibility	**v**	Adverse effects following vaccination are well-known phenomena. Myocarditis following vaccination was reported for other vaccines (smallpox)
7	Coherence	**v**	Some biological mechanisms were suggested to explain the observed association, and a special effort was made to rule out other potential causes for myocarditis
8	Experiment	**x**	Not observed in company's RCTs, but the numbers in the RCT setting were much too small for detection of myocarditis
9	Analogy	**v**	Other vaccines (e.g., smallpox) were previously reported to be associated with myocarditis as an adverse effect. Another mRNA vaccine was reported to be associated with myocarditis.

Supplementary Table S4. Sample ssupplementary table on the representativeness of study participants.

Category	Example
Condition under investigation	Myocarditis
Special considerations	Post-vaccination with BNT162b2 against COVID-19. There are also reports related to the other mRNA vaccine (Moderna)
Gender	Post-vaccination myocarditis affects men more than women (ratio of 12:1)
Age	Prevalence similar in 12−15-year-old
Race or ethnic group	Jews (Sephardic and Ashkenazi), Moslems, and Others
Geography	Israel
Other considerations	Post-vaccination myocarditis occurs mostly after the second vaccination and mostly in males
Overall representativeness of this observation	The ratio of men to women among participants in the present trial was as expected based on the previous study.[2] Biologic gender was reported by the physicians. Patients with post-vaccination myocarditis have been reported in Israel, Europe, Asia, and the US. Frequency by ethnic group in Israel is representative of the proportions of Jews (75%) and Arabs (20%) in the general population, including Jews of Ashkenazi or Sephardic origin. Causes of myocarditis were consistent with epidemiologic and registry data where these were available from European countries, the US, and China. No patient was reported thus far in Africa.

Appendix: Myocarditis classifications

Case definition by the recommended classifications based on Brighton Collaboration Myocarditis Case Definition (Pandemic Emergency Response Process).[1]

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 18 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

3. 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).**