Incidence, follow-up, and pathophysiology of myocarditis following mRNA vaccine in Israel: Results of an Active Surveillance

January 2023

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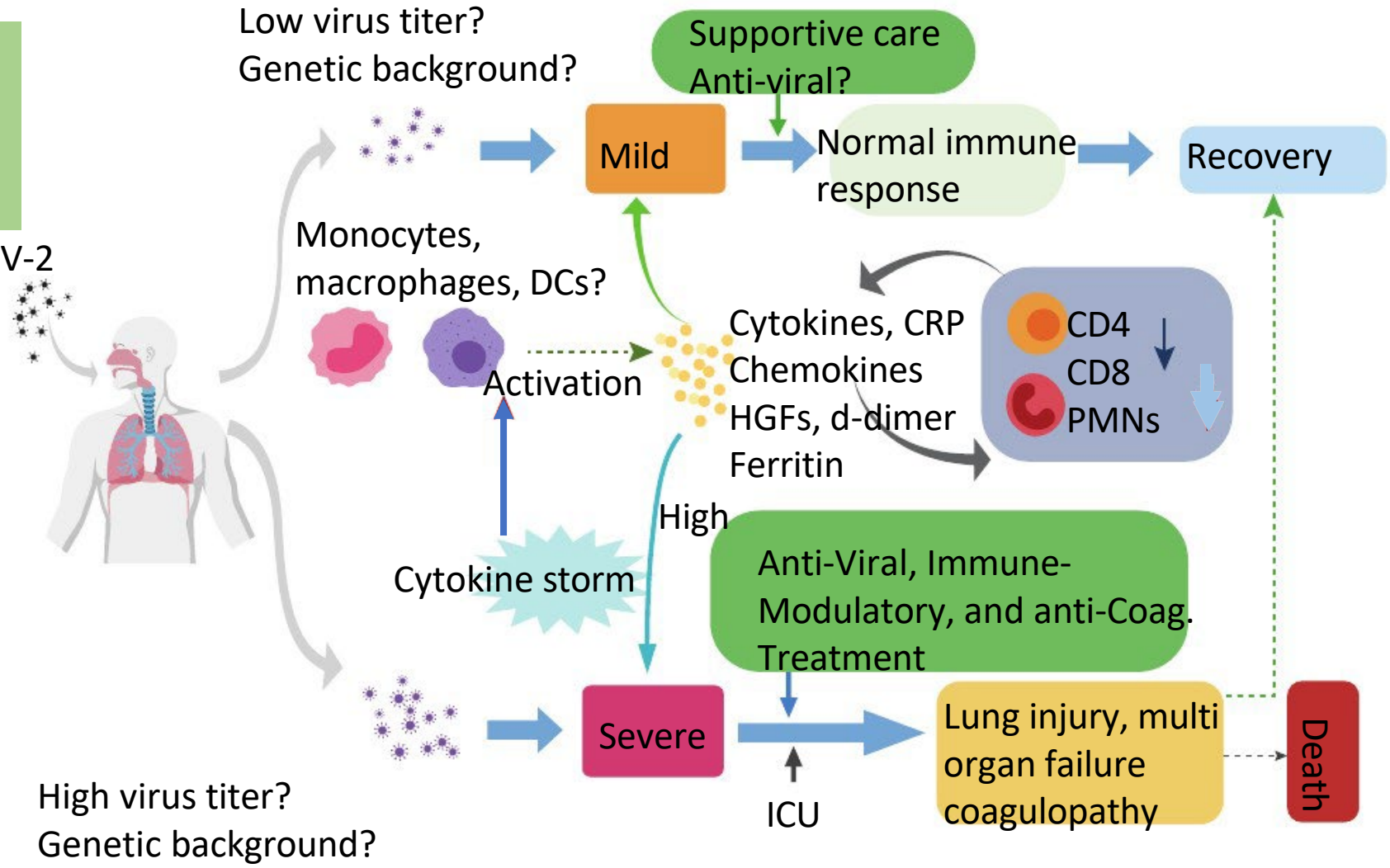
Disclosures

- D Mevorach id the Founder and CSO of Enlivex Therapeutics

Cytokine storm and pathophysiology of COVID 19

Prevention:
Hygiene, Mask, Distance
Immunization?
Post exposure?

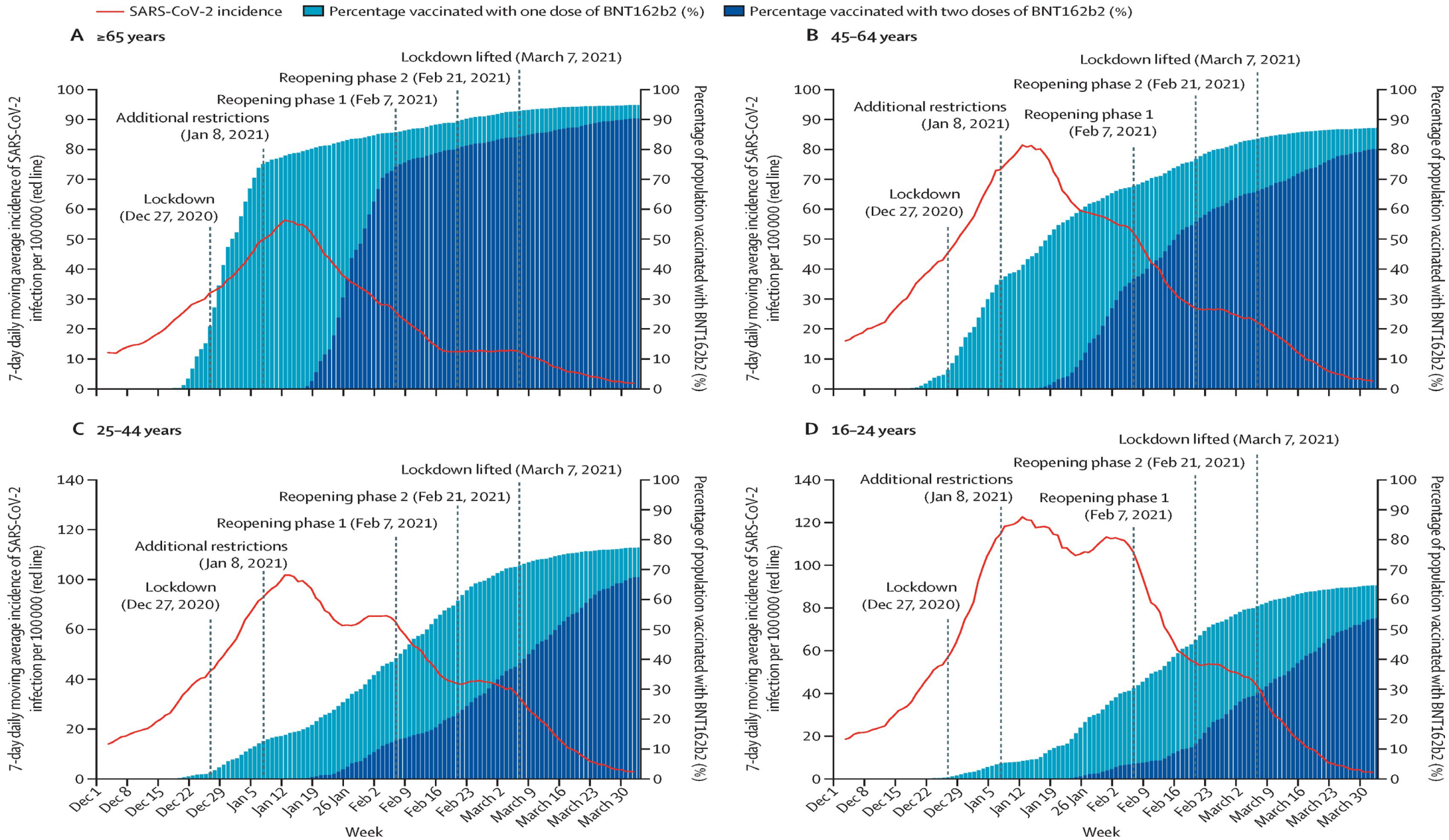


	Date	Milestone
2020	Dec 1	Covid-19 illness documented (unpublicized Nov 17th)
2021	Jan 10	SARS-CoV-2 virus sequenced
	Jan 15	NIH designs mRNA vaccine in collaboration with Moderna
	Mar 16	Moderna Phase 1|2 trial begins
	May 2	Pfizer/BioNTech Phase 1|2 trial begins
	July 14	Moderna Phase 1|2 trial published in NEJM
	July 27, 28	Moderna and Pfizer/BioNTech Phase 3 trial begins
	Aug 12	Pfizer/BioNTech Phase 1|2 published in Nature
	October 22,27	Enrollment in both Phase 3 trials complete; >74,000 participants
	Nov 9	Pfizer/BioNTech announces interim analysis efficacy > 90%
	Nov 16	Moderna announces interim analysis efficacy 94.5%
	Nov 18	Pfizer/BioNTech announces 95% efficacy as final result
	Nov 20	1st EUA submitted by Pfizer/BioNTech
	Nov 27	Distribution of vaccine by UAL charter flights throughout US
	Dec 10	FDA External review of Pfizer/BioNTech EUA
	Dec 11	Phase 1a Vaccination begins for health care professionals*

*Provisional on positive external review

Vaccines against COVID19

Country & Developer		How It Works	Price ($)	Status
USA and Germany	Pfizer-BioNTech	mRNA, single-stranded RNA	30	Approved in U.S., other countries. Emergency use in E.U., other countries.
USA	Moderna	mRNA, single-stranded RNA	35	Approved in Switzerland. Emergency use in U.S., E.U., other countries.
USA & Belgium	Johnson & Johnson	DS DNA in adenovirus Ad26	10	Emergency use in U.S., E.U., other countries.
UK & Sweden	Oxford-AstraZeneca	chimpanzee adenovirus, ChAdOx1	5	Approved in Brazil. Emergency use in U.K., E.U., other countries.
USA	Novavax	Spike Protein	?	Emergency use in U.S
Russia	Gamaleya	DS DNA in adenovirus Ad26, Ad5	3	Emergency use in Russia, other countries.
China	CanSino	DS DNA in adenovirus Ad5		Approved in China. Emergency use in other countries.
Russia	Vector Institute	Spike Protein	3	Approved in Turkmenistan. Early use in Russia.
China	Sinopharm	Inactivated Sars-2	?	Approved in China, U.A.E., Bahrain. Emergency use in other countries.
China	Sinovac	Inactivated Sars-2	?	Approved in China. Emergency use in other countries.
China	Sinopharm-Wuhan	Inactivated Sars-2	?	Approved in China. Limited use in U.A.E
India	Bharat Biotech	Inactivated Sars-2	?	Emergency use in India, other countries.



Haas et al, Lancet May 15, 2021

Pfizer-BioNTech BNT162b2 vaccine in Israel

- Following Emergency Use Authorization* of the Pfizer-BioNTech BNT162b2 vaccine by the FDA, authorization was granted for use in Israel and on December 20, 2020, a national vaccination campaign was initiated.

*Emergency Use Authorization: Pfizer-BioNTech COVID-19 vaccine. 2021; Washington, D.C., U.S.A.: U.S. Food and Drug Administration (FDA). Available online: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine. Accessed July 16, 2021

- On January 10th, 2021, the first patient ever with post-vaccination myocarditis was hospitalized at the Department of Medicine B, Hadassah Medical Center, Ein Karem, Jerusalem and was reported the MoH in Israel and WHO (as well as by : @DrorMevorach).
- The MoH then established a special committee to follow-up possible myocarditis cases.

A nationwide active surveillance of myocarditis

- Beginning in December 2020 a campaign of passive surveillance was conducted for adverse events following immunization within 21 days following the first dose and 30 days following the second dose and reported to the Ministry of Health (MoH) by healthcare providers as required by Israeli law.
- Following few cases of myocarditis that were followed by a special committee of the MoH, MoH subsequently initiated an active surveillance beginning retrospectively from December 2020 by requesting that all hospitals report cases of myocarditis, with or without pericardial effusion and regardless of vaccination status.
- Cases of suspected myocarditis are almost always hospitalized in Israel, and therefore surveillance data should approximate all cases of myocarditis during the period of active surveillance.

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ORIGINAL ARTICLE

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

D. Mevorach, E. Anis, N. Cedar, M. Bromberg, E.J. Haas, E. Nadir, S. Olsha-Castell, D. Arad, T. Hasin, N. Levi, R. Asleh, O. Amir, K. Meir, D. Cohen, R. Dichtiar, D. Novick, Y. Hershkovitz, R. Dagan, I. Leitersdorf, R. Ben-Ami, I. Miskin, W. Saliba, K. Muhsen, Y. Levi, M.S. Green, L. Keinan-Boker, and S. Alroy-Preis

ABSTRACT

BACKGROUND

Approximately 5.1 million Israelis had been fully immunized against coronavirus disease 2019 (Covid-19) after receiving two doses of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) by May 31, 2021. After early reports of myocarditis during adverse events monitoring, the Israeli Ministry of Health initiated active surveillance.

METHODS

OCT 06, 2021

Active surveillance of myocarditis: Methods

- The diagnostic criteria for myocarditis were adapted from the case definition and classification of the Brighton Collaboration Myocarditis Case Definition. Myocarditis/pericarditis case definition. 2021; Decatur, GA, USA: Brighton Collaboration of the Task Force for Global Health. Available online: https://brightoncollaboration.us/myocarditis-case-definition-update/. Accessed July 25, 2021.
- Cases were also compared to classifications of myocarditis issued by the CDC for adverse events following smallpox vaccination. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Morbid Mortal Wkly Rep 2006; 55(RR01):1-16 Washington, DC, USA: Centers for Disease Control (CDC), US Department of Health and Human Services (HHS). Available online: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm#top. Accessed July 22, 2021.

- Cases were classified as definitive (biopsy is not mandatory), probable, possible, cases with insufficient data, or cases that were ruled out as myocarditis.

Active surveillance of myocarditis: Methods (III)

To assess the incidence of myocarditis in vaccinated individuals, three approaches were used:

- **Rate ratio** between vaccinated and nonvaccinated individuals.
- **Overall, risk difference** between first and second vaccines.
- **Observed-to-expected ratio.** We compared the observed incidence to the expected incidence (standardized incidence ratios (SIR) in previous years.

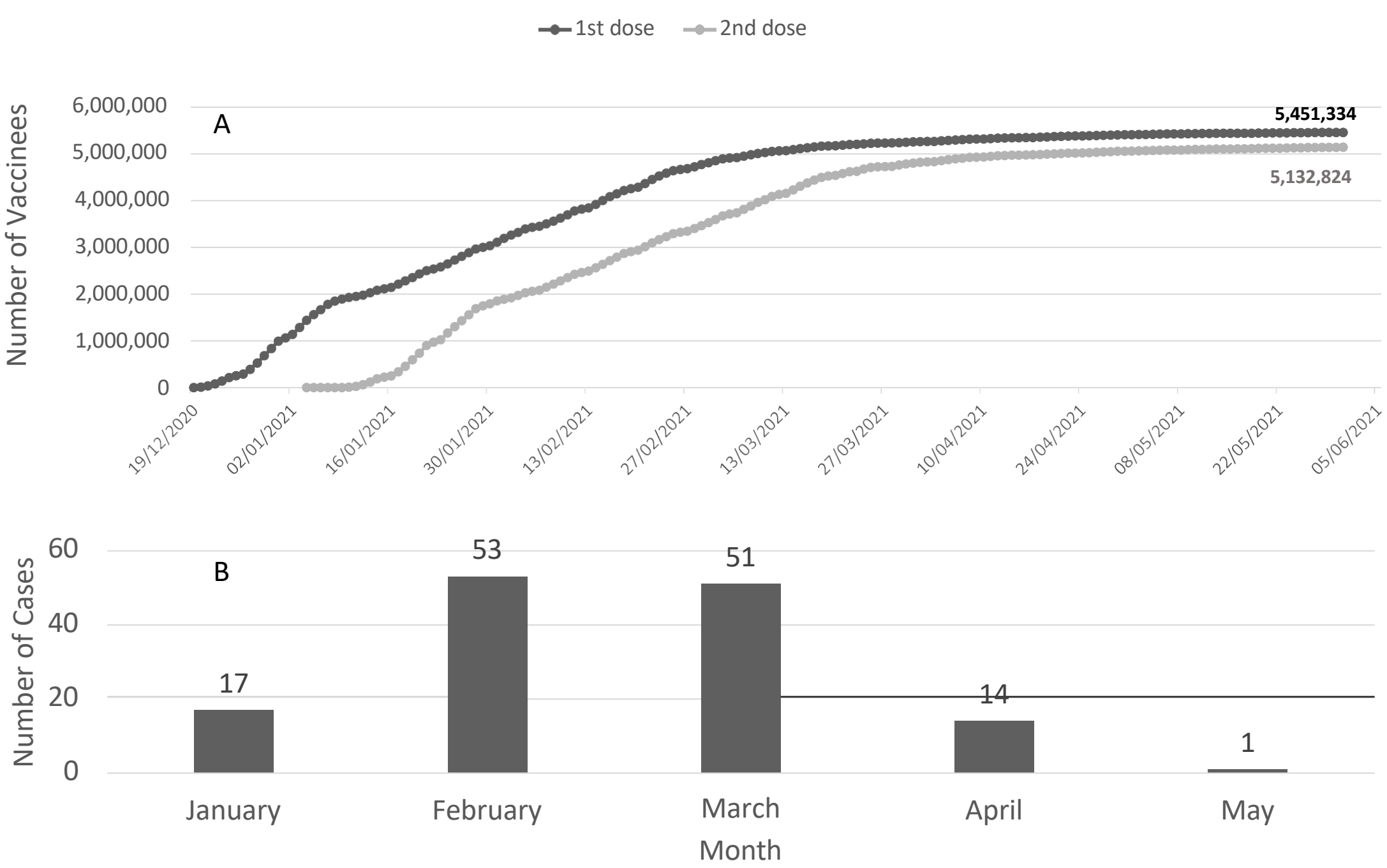
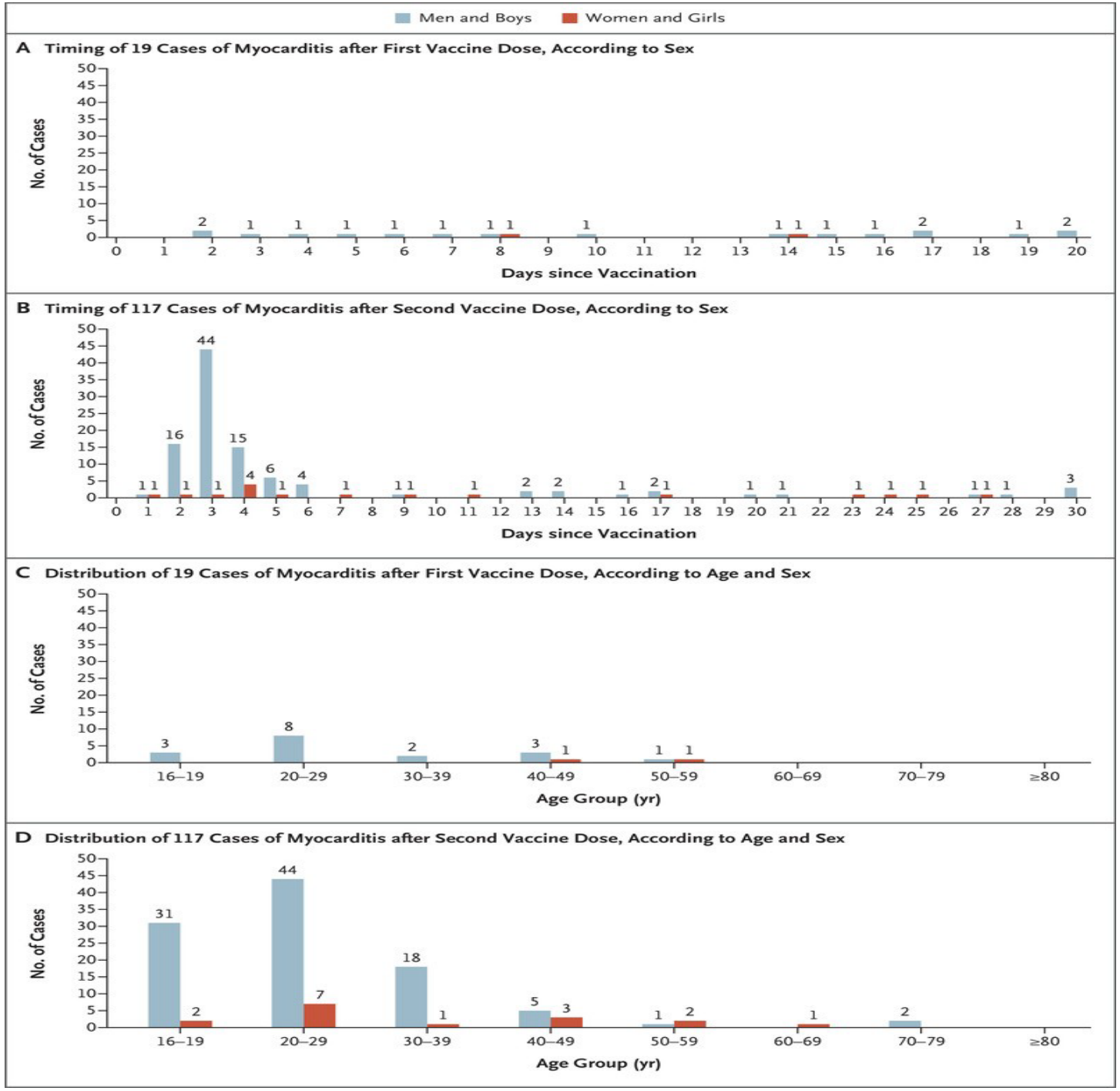


Figure S3. Mevorach et al.



Gender & Timing: First dose

Gender & Timing : Second dose

Gender & Age: First dose

Gender & Age: Second dose

Mevorach et al. N Engl J Med, October 2021

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%)

Mevorach et al. N Engl J Med, October 2021: Supplementary Appendix

Table 5. Rate Ratios for a Diagnosis of Myocarditis within 30 Days after the Second Dose of Vaccine, as Compared with Unvaccinated Persons (January 11 to May 31, 2021).

Age and Sex	Vaccinated Group		Unvaccinated Group		Rate Ratio (95% CI)
	Person-Days of Follow-up	Cases	Person-Days of Follow-up	Cases	
			number		
All recipients*	149,786,065	117	296,377,727	98	2.35 (1.10–5.02)
16–19 yr					
Male	6,018,541	31	19,135,706	11	8.96 (4.50–17.83)
Female	6,033,192	2	17,768,696	2	2.95 (0.42–20.91)
20–24 yr					
Male	7,088,335	27	20,926,320	13	6.13 (3.16–11.88)
Female	6,889,399	5	20,832,407	2	7.56 (1.47–38.96)
25–29 yr					
Male	6,590,263	18	20,944,595	16	3.58 (1.82–7.01)
Female	6,417,564	1	20,943,920	0	0
≥30 yr					
Male	53,577,403	26	82,419,957	40	1.00 (0.61–1.64)
Female	57,171,368	7	93,406,126	14	0.82 (0.33–2.02)

* Data for all vaccine recipients have been weighted according to age and sex.

Mevorach et al. N Engl J Med, October 2021

Risk of Myocarditis within 21 Days after the First or Second Dose of Vaccine, According to Age and Sex

Table 3. Risk of Myocarditis within 21 Days after the First or Second Dose of Vaccine, According to Age and Sex.*

Age and Sex	First Dose			Second Dose			Risk Difference (95% CI)
	Recipients	Cases	Risk per 100,000 Persons	Recipients	Cases	Risk per 100,000 Persons	
	number			*number*			*no./100,000 persons*
Male recipients							
All ages	2,668,894	17	0.64	2,507,210	96	3.83	3.19 (2.37 to 4.02)
16–19 yr	224,518	3	1.34	199,115	30	15.07	13.73 (8.11 to 19.46)
20–24 yr	261,741	5	1.91	239,396	26	10.86	8.95 (4.42 to 13.55)
25–29 yr	246,638	3	1.22	228,988	16	6.99	5.77 (2.02 to 9.58)
30–39 yr	491,126	2	0.41	461,044	17	3.69	3.28 (1.41 to 5.18)
40–49 yr	458,268	3	0.65	433,069	5	1.15	0.50 (–0.82 to 1.84)
≥50 yr	986,603	1	0.10	945,598	2	0.21	0.11 (–0.29 to 0.52)
Female recipients							
All ages	2,773,802	2	0.07	2,618,425	12	0.46	0.39 (0.10 to 0.68)
16–19 yr	219,460	0	0	199,706	2	1.00	1.00 (–0.63 to 2.72)
20–24 yr	250,556	0	0	231,960	5	2.16	2.16 (0.13 to 4.24)
25–29 yr	235,575	0	0	219,113	0	0	0 (–0.83 to 0.89)
30–39 yr	481,045	0	0	451,791	1	0.22	0.22 (–0.37 to 0.84)
40–49 yr	472,083	1	0.21	444,916	2	0.45	0.24 (–0.61 to 1.11)
≥50 yr	1,115,083	1	0.09	1,070,939	2	0.19	0.10 (–0.26 to 0.46)

* Among vaccine recipients of all ages and both sexes, the overall difference in the incidence of myocarditis after the second dose as compared with the incidence after the first dose was 1.76 (95% confidence interval [CI], 1.33 to 2.19). The widths of the confidence intervals have not been adjusted for multiple testing.

Mevorach et al. N Engl J Med, October 2021

Observed to expected ratio. Standardized Incidence Ratios (SIRs) and 95%CI for myocarditis by vaccine dose, age, and gender – all cases diagnosed within 21d and 30d following the first and second vaccination, respectively

Table 4. Standardized Incidence Ratios for 151 Cases of Myocarditis, According to Vaccine Dose, Age, and Sex.

Age and Sex	First Dose			Second Dose		
	Observed Cases	Expected Cases per 2017–2019 Reference*	Standardized Incidence Ratio (95% CI)	Observed Cases	Expected Cases per 2017–2019 Reference*	Standardized Incidence Ratio (95% CI)
	number			*number*		
All recipients†	25	17.55	1.42 (0.92–2.10)	126	23.43	5.34 (4.48–6.40)
16–19 yr						
Male	3	1.86	1.62 (0.32–4.72)	32	2.35	13.60 (9.30–19.20)
Female	0	0.23	0	2	0.30	6.74 (0.76–24.35)
20–24 yr						
Male	5	2.33	2.14 (0.69–5.00)	26	3.05	8.53 (5.57–12.50)
Female	1	0.42	2.37 (0.03–13.20)	6	0.56	10.76 (3.93–23.43)
25–29 yr						
Male	3	2.17	1.39 (0.28–4.05)	20	2.87	6.96 (4.25–10.75)
Female	0	0.30	0	1	0.39	2.54 (0.03–14.14)
≥30 yr						
Male	10	8.13	1.23 (0.59–2.26)	32	11.04	2.90 (1.98–4.09)
Female	3	2.11	1.42 (0.29–4.15)	7	2.87	2.44 (0.98–4.09)

* Reference data regarding the background incidence of myocarditis were extracted from the Israel National Hospital Discharge Database for the years 2017 through 2019.

† Data are listed for the 151 vaccine recipients in whom myocarditis was diagnosed at any level of certainty within 21 days after the first dose and 30 days after the second dose; data for all vaccine recipients have been weighted according to age and sex.

Mevorach et al. N Engl J Med, October 2021

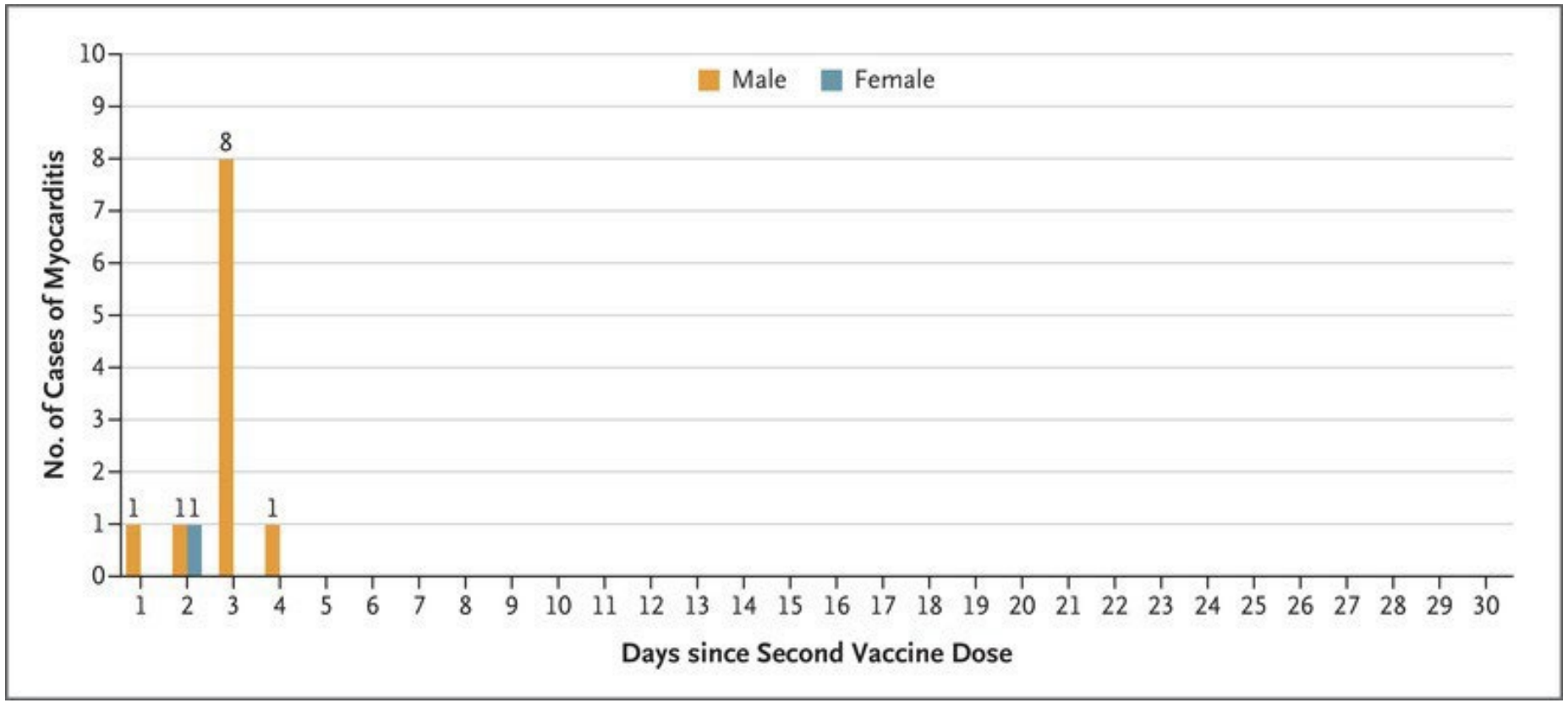
Mevorach et al. The New England Journal of Medicine January 26, 2022

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Myocarditis after BNT162b2 Vaccination in Israeli Adolescents

TO THE EDITOR: Using an active nationwide surveillance system administered by the Israeli Ministry of Health, we previously found a higher incidence of myocarditis among persons 16 years of age or older who had received the BNT162b2 vaccine (Pfizer–BioNTech) than among historical controls and unvaccinated persons; the incidence was highest among young male recipients.[1] The Food and Drug Administration recently granted emergency use authorization for the two-dose regimen of the BNT162b2 vaccine in adolescents with myocarditis occurring within 21 days after receipt of the first vaccine dose or within 30 days after receipt of the second dose are shown in Table S1 in the Supplementary Appendix. These 13 cases were classified as probable or definitive myocarditis according to the case definition. All the cases were clinically mild, involving a mean duration of hospitalization of 3.1 days (range, 1 to 6) and no readmissions during 30 days of follow-up. Symptoms at presentation, laboratory features, and echocar-


Male
Female
No. of Cases of Myocarditis
0
1
2
3
4
5
6
7
8
9
10
1
11
8
1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Days since Second Vaccine Dose

Myocarditis after BNT162b2 Vaccination in Adolescents 12 to 15 Years of Age

- Risk estimates in the 21 days following doses 1 and 2, respectively, were overall 0.56/100,000 persons and 8.09/100,000 for males, and 0/100,000 and 0.69/100,000 for females.

- The risk of myocarditis following the second vaccine dose in males ages 12−15 was estimated as 1:12,369 and for females, 1:144,439. The risks were lower than for males aged 16−29 in our previous report,1 but slightly higher than U.S. Centers for Disease Control and Prevention estimates of approximately 1:80,000 cases after the second dose in individuals aged 12−39, and approximately 1:15,000 and 1:19,000 for males aged 12−17 and 18−24, respectively.3,4 These differences may be explained by the use of active surveillance in our population. A possible explanation for the absence of cases of myocarditis in a phase 3 trial of the vaccine, is the relatively small number of 1131 vaccinated adolescents between ages 12 and 15, of whom only 567 were male.5

SARS-CoV-2 Vaccination and Myocarditis in a 2 Nordic Cohort study of 23 Million residents
Karlstad/Hovi, and Husby/Hviid/Ljung et al. Jama-Cardiology 2022

- Norwegian Institute of Public Health, Department of Chronic Diseases, Oslo, Norway
- Finnish Institute for Health and Welfare, Department of Public Health and Welfare, 8 Helsinki, Finland
- Statens Serum Institut, Department of Epidemiology Research, Copenhagen, Denmark
- Imperial College London, Department of Epidemiology and Biostatistics, London,
- Swedish Medical Products Agency, Division of Licensing, Uppsala, Sweden
- Finnish Institute for Health and Welfare, Health Security, Helsinki, Finland
- Norwegian Research Centre for Women's Health, Oslo University Hospital, Oslo
- Swedish Medical Products Agency, Division of Use and Information, Uppsala, Sweden
- Finnish Institute for Health and Welfare, Information Services, Helsinki, Finland
- Pharmacovigilance Research Center, Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark
- Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden

SARS-CoV-2 Vaccination and Myocarditis in a 2 Nordic Cohort study of 23 Million residents.
Karlstad/Hovi, and Husby/Hviid/Ljung et al. JAMA-Cardiology 2022

- Their findings: Among 23.1 million residents (81% vaccinated by study end), 1,077 myocarditis and 1,149 pericarditis events. Within the 28-day period, second dose of BNT162b2 and mRNA-1273 were for males and females 12 years and older combined, associated with higher risk of myocarditis, adjusted RRs 1.8 (95% CI, 1.4-2.1) and 6.6 (4.6-9.3), respectively.
- Among males 16-24 years RRs were 5.3 (3.7-7.7) and 13.8 (8.1- 84 23.7), and excess events 5.6 (3.7-7.4) and 18.4 (9.1-27.7) per 100,000 vaccinee, respectively. RRs for the 7-day period were higher. Estimates for pericarditis were similar.

- In comparison to a nationwide active surveillance (Mevorach et al.) with verification of the diagnoses adjusted RRs 1.76 (Mevorach et al.) versus 1.8 in the current manuscript) were similar for BNT162b2. However, among males 16-24 years RRs were 7.54 (Mevorach et al.) versus 5.3 in the current manuscript suggesting a bit lower reported incidence in the current manuscript. These differences may arise from the method of collection but possibly also from predisposition differences.

Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents

Mansanguan et al. Trop Med Infect Dis 2022 Aug 19;7(8):196

- This prospective cohort study enrolled students aged 13-18 years from two schools, who received the second dose of the BNT162b2 mRNA COVID-19 vaccine.
- Data including demographics, symptoms, vital signs, ECG, echocardiography, and cardiac enzymes were collected at baseline, Day 3, Day 7, and Day 14 (optional) using case record forms.
- We enrolled 314 participants; of these, 13 participants were lost to follow-up, leaving 301 participants for analysis.

Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents

Mansanguan et al. Trop Med Infect Dis 2022 Aug 19;7(8):196

- The most common cardiovascular signs and symptoms were tachycardia (7.64%), shortness of breath (6.64%), palpitation (4.32%), chest pain (4.32%), and hypertension (3.99%).
- Seven participants (2.33%) exhibited at least one elevated cardiac biomarker or positive lab assessments.
- Cardiovascular manifestations were found in 29.24% of patients, ranging from tachycardia or palpitation to myopericarditis. Myopericarditis was confirmed in one patient after vaccination (0.3%)

Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents

Mansanguan et al. Trop Med Infect Dis 2022 Aug 19;7(8):196

- Conclusions:
- In a prospective study of teenager's cohort of second vaccination, 1:301 (0.3%) were found with "mild myocarditis", (for a comparison we have reported 1:6600. this is 20 times higher).
- “We found the risk of these symptoms to be not as low as reported elsewhere, but in all cases, symptoms were mild with full recovery within 14 days.”

Limitations of the study by Mansanguan et al.

- Myocarditis was not validated by myocardial biopsy, and acquisition bias could be present as clinical assessors were not masked to whether the individual was vaccinated or not.
- Misclassification may have taken place. The diagnostic criteria for myocarditis were NOT an acceptable classification case definition:classification of the Brighton Collaboration Myocarditis Case Definition or Smallpox definitions).
- Myocarditis patients were those with the presence or worsening of more than one of the following clinical symptoms along with evidence of inflammation: (1) chest pain, pressure, or discomfort; (2) dyspnea, shortness of breath, or pain with breathing; (3) palpitation; or (4) syncope and more than one new finding of: (a) troponin level above upper normal limit of normal; (b) abnormal ECG or rhythm monitoring consistent with myocarditis; (c) abnormal cardiac function or wall motion on echocardiography; (d) cardiac magnetic resonance imaging (cMRI) findings consistent with myocarditis and no identifiable cause for symptoms and findings.
- The sample error may be relevant as this is a small study and the rate of 1:301 can easily be 1:600 in a bigger study and even lower.

Circulation September 2022

RESEARCH LETTER

Myocarditis After *BNT162b2* COVID-19 Third Booster Vaccine in Israel

Dror Mevorach, MD*; Emilia Anis, MD, MPH*; Noa Cedar, MPH†; Tal Hasin, MD†; Michal Bromberg, MD, MPH; Lital Goldberg, MD, MPH‡; Nir Levi, MD‡; Ofer Perzon, MD; Nur Magadle, MD; Barhoum Barhoum, MD, Elchana Parnassa, MD; Rita Dichtiar, MPH; Yael Hershkovitz, MSc; Manfred S. Green, MB, ChB, PhD; Nachman Ash, MD; Lital Keinan-Boker, MD, PhD§; Sharon Alroy-Preis, MD, MPH§

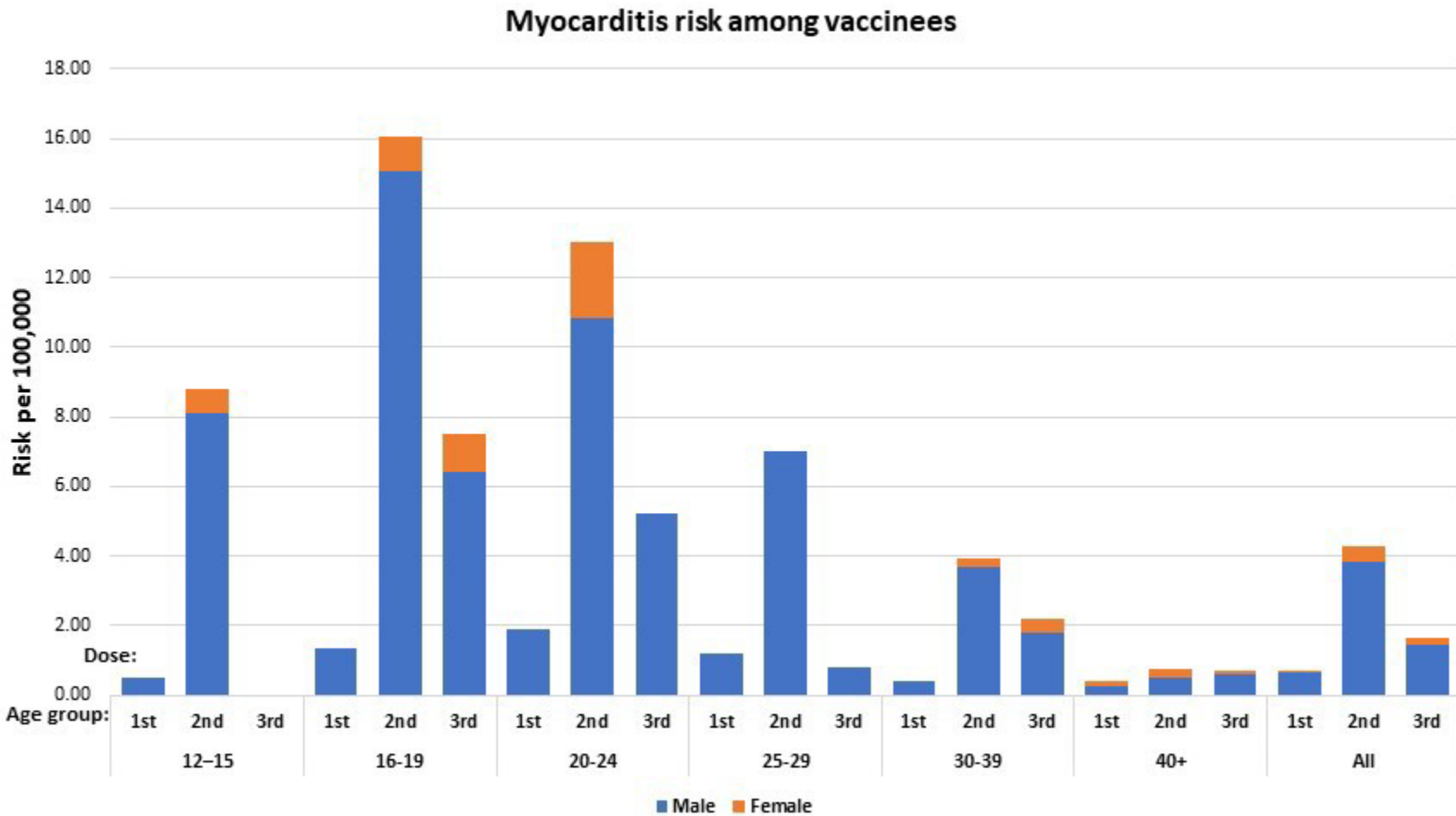
The efficacy of the Pfizer BioNTech BNT162b2 vaccine has been demonstrated in clinical trials and postvaccination observational studies. However, effectiveness had declined, and vaccine-induced immunity was waning.[1] On November 17, 2021, the US Food and Drug Administration expanded the Emergency Use Authorization for the Pfizer and Moderna coronavirus disease 2019

During the surveillance period, 3 944 797 individuals (1 919 453 male, 48.7%) received a booster dose. Ninety-one cases of myocarditis were reported, including 35 cases within 30 days of booster vaccination. Among them, 28 were probable or confirmed myocarditis; 18 of 28 occurred during the first week after the booster. All 28 cases were clinically mild, and patients recovered

Myocarditis After *BNT162b2* COVID-19 3rd Booster Vaccine in Israel

- Compared to vaccine dose 1, for males the overall risk differences per 100,000 were 0.63 **(**95%CI 0.03 to 1.27), with higher risk mainly in 16-19 years young males, 5.25 (95%CI 0.35 to 11.46); and 20-24 years, 2.26 (95%CI -1.53 to 6.77).

- Observed-to-expected myocarditis incidence in the 30 days following the booster vaccine dose was SIR=2.29 (95% CI 1.56 to 3.23) and SIR=1.03 (95% CI 0.21 to 3.00) in males and females, respectively, with significantly elevated ratios for males aged 16−19 (SIR=5.45, 95%CI 1.99-11.87), 20−24 (SIR=4.68, 95%CI 2.01-9.22) and 40+ (SIR=2.59, 95%CI 1.29 to 4.63) years.


Myocarditis risk among vaccinees
Risk per 100,000
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Dose:
Age group:
1st 2nd 3rd 1st 2nd 3rd 1st 2nd 3rd 1st 2nd 3rd 1st 2nd 3rd 1st 2nd 3rd 1st 2nd 3rd
12–15
16-19
20-24
25-29
30-39
40+
All
Male
Female

Adverse effects (AEs)in vaccination: Defining the problem

- Are AE’s mild or severe? Fatal or transient?
- Are AE’s :

Very likely/ Probable/Possible/Unlikely/Unrelated/Unclassifiable

- Are AE’s collected passively or actively?
- Are AE’s idiosyncratic or general? (example anaphylaxis)
- Risk/benefit?
- How would AE’s change vaccination policy? Public behavior?

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RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

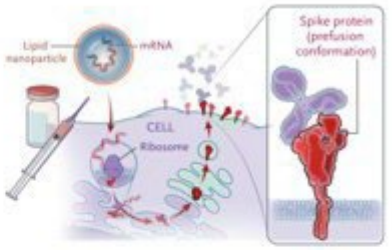
Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.

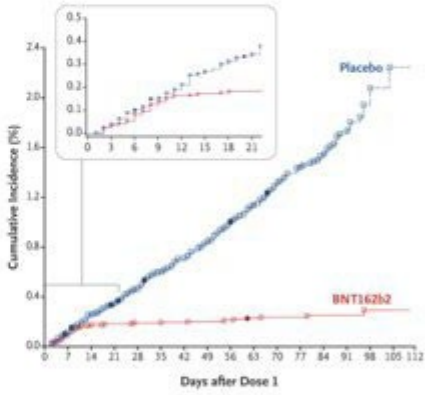
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

Links: Full article | Quick Take | Editorial





Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

CONCLUSIONS

Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)

The mechanism of vaccine-induced myocarditis

Related to the active component of the vaccine, the mRNA sequence that codes for the spike [S] protein of SARS-CoV-2?

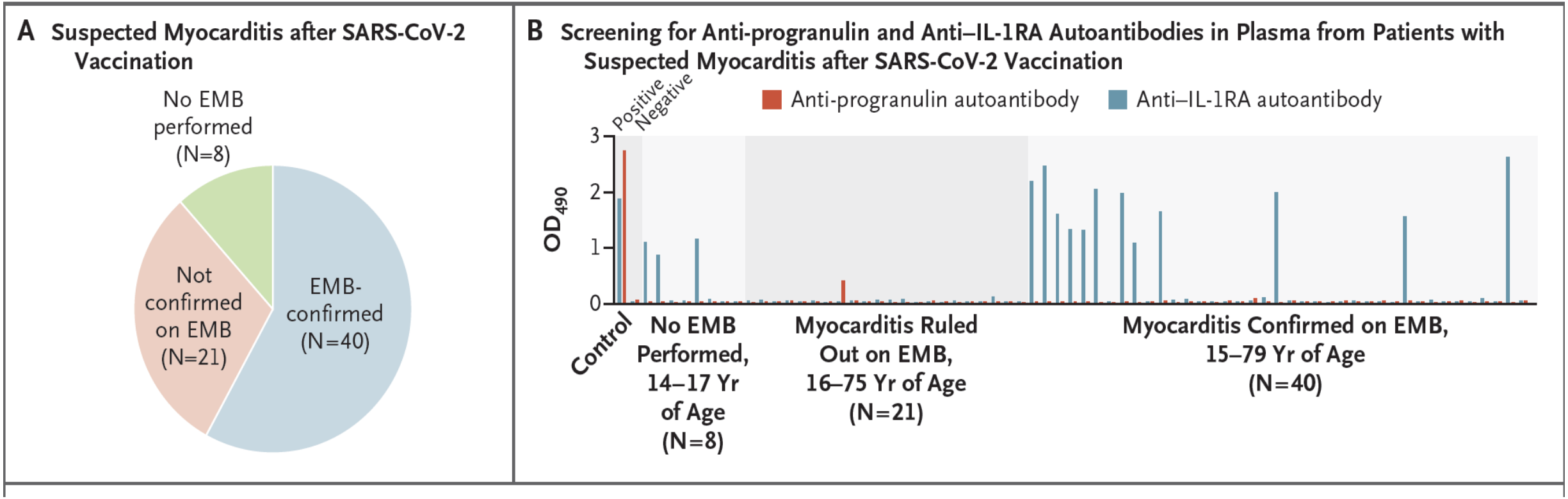
Related to the immune response that follows vaccination?

- mRNA vaccines tend to act as their own adjuvant and stimulate a further immune response that improves their efficacy.
- RNA is encapsulated in liposomes to avoid degradation by RNases, and the molecule is delivered inside target cells following a process of endocytosis.
- mRNA is then translated into immunogenic proteins by cell ribosomal processing. Prior to translation, mRNA may bind pattern recognition receptors (PRRs) in endosomes or cytosol.

The mechanism of vaccine-induced myocarditis

- Toll-like receptors (TLR)3, TLR7, and TLR8 are able to recognize chains of double-stranded RNA (dsRNA) or single-stranded RNA (ssRNA) in endosomes, while retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) may detect short and long filaments of dsRNA in the cytosol.
- In any of these scenarios, the result would be activation of several pro-inflammatory cascades, including inducing expression of complement components, assembly of inflammasome platforms, type I interferon (IFN) response, and nuclear activation of nuclear factor (NF)-kB.

IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination



Lorenz et al. NEJM; September 21, 2022

Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis

Circulation. 2023;0

Abstract

METHODS:

From January 2021 through February 2022, we prospectively collected blood from 16 patients who were hospitalized at Massachusetts General for Children or Boston Children's Hospital for myocarditis, presenting with chest pain with elevated cardiac troponin T after SARS-CoV-2 vaccination. We performed extensive antibody profiling, including tests for SARS-CoV-2–specific humoral responses and assessment for autoantibodies or antibodies against the human-relevant virome, SARS-CoV-2–specific T-cell analysis, and cytokine and SARS-CoV-2 antigen profiling. Results were compared with those from 45 healthy, asymptomatic, age-matched vaccinated control subjects.

RESULTS:

Extensive antibody profiling and T-cell responses in the individuals who developed postvaccine myocarditis were essentially indistinguishable from those of vaccinated control subjects, despite a modest increase in cytokine production. A notable finding was that markedly elevated levels of full-length spike protein (33.9±22.4 pg/mL), unbound by antibodies, were detected in the plasma of individuals with postvaccine myocarditis, whereas no free spike was detected in asymptomatic vaccinated control subjects (unpaired *t* test; $P<0.0001$).

CONCLUSIONS:

Immunoprofiling of vaccinated adolescents and young adults revealed that the mRNA vaccine–induced immune responses did not differ between individuals who developed myocarditis and individuals who did not. However, free spike antigen was detected in the blood of adolescents and young adults who developed post-mRNA vaccine myocarditis, advancing insight into its potential underlying cause.

Genetic evaluation

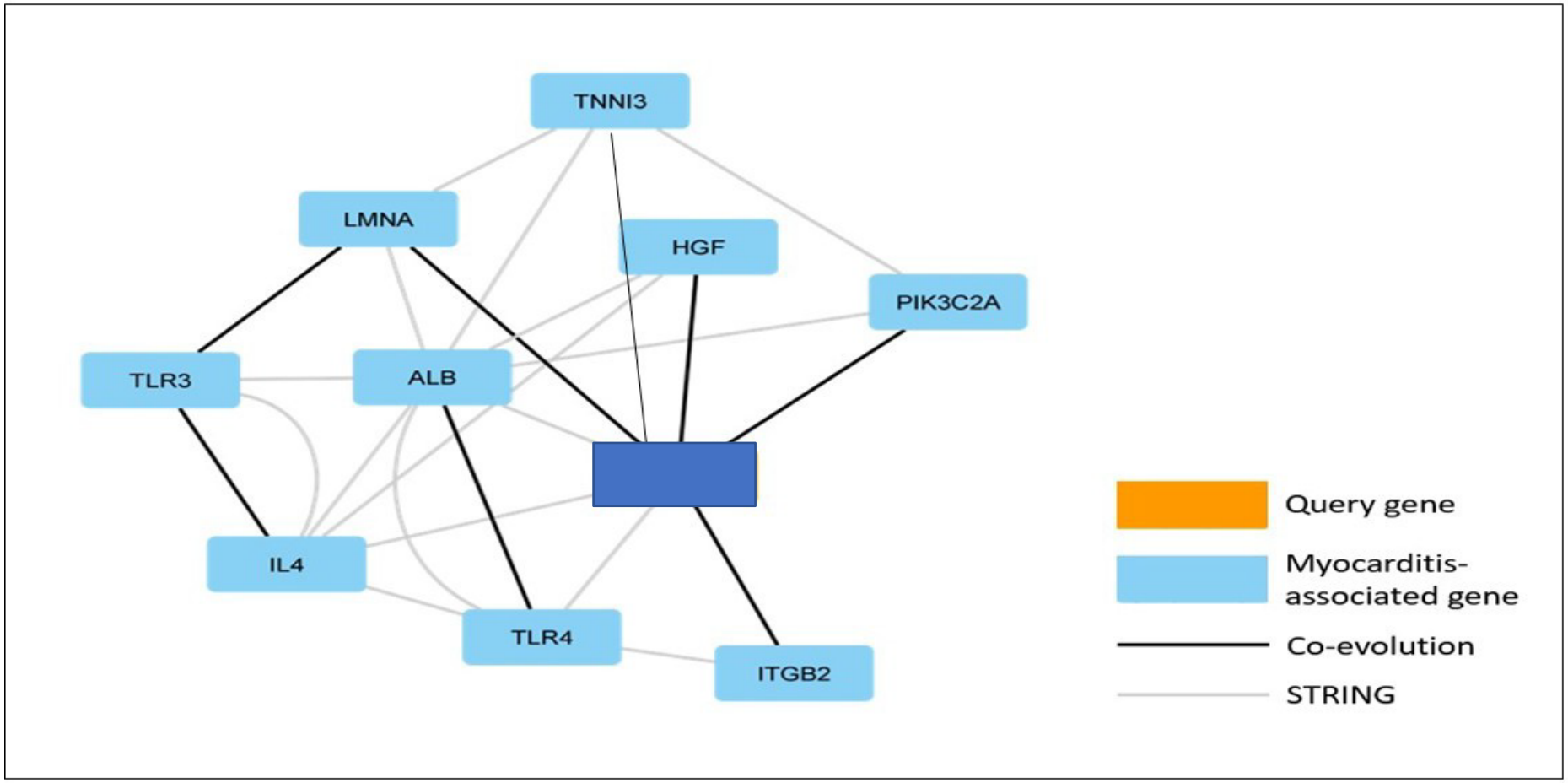


Fig.6

Follow up

- We have a database of >200 patients with vaccine induced myocarditis
- We follow the patients, using questionnaires, physical exam, blood tests, echocardiogram and MRI

Acknowledgments:

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