

- on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of kawasaki disease: a Scientific Statement for Health Professionals From the American Heart Association. *Circulation*. 2017;135:e927–e999.
9. Harahsheh AS, Hom LA, Clauss SB, et al. The impact of a designated cardiology team involving telemedicine home monitoring on the care of children with single-ventricle physiology after norwood palliation. *Pediatr Cardiol*. 2016;37:899–912.
10. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. *JAMA Pediatr*. 2021;175:837–845.

APPENDIX

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POPULATION-BASED INCIDENCE OF MYOPERICARDITIS AFTER COVID-19 VACCINATION IN DANISH ADOLESCENTS

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Abstract: In this prospective nationwide multicenter study from Denmark, myopericarditis after Pfizer-BioNTech mRNA COVID-19 vaccination was identified in 13 males and 2 females between May 15 and September 15, 2021, among 133,477 vaccinated males and 127,857 vaccinated females 12–17 years of age, equaling 97 males and 16 females per million. In conclusion, the incidence of myopericarditis after COVID-19 vaccination among males appears higher than reports from the United States.

Key Words: mRNA COVID-19 vaccine, myopericarditis, adolescents
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Myopericarditis is a complication to mRNA COVID-19 vaccines, especially in male adolescents and young adults.¹ According to the US Vaccine Adverse Event Reporting System (VAERS), the rate of myopericarditis has been reported to be 56–69 per million vaccinated males 12–17 years of age and 8–10 per million vaccinated females 12–17 years of age.¹ However, as underreporting is a limitation of VAERS, the estimates are encumbered with uncertainty.^{1,2}

In Denmark, the Pfizer-BioNTech mRNA COVID-19 vaccination was recommended from May 15, 2021, in individuals 16–17 years of age and from July 15, 2021, in individuals 12–15 years of age. We aimed to estimate the incidence of myopericarditis in adolescents after mRNA COVID-19 vaccination among vaccinated individuals based on a nationwide prospective population-based cohort study with detailed clinical phenotyping.

MATERIALS AND METHODS

The study was a prospective population-based cohort study of all individuals 12–17 years of age hospitalized due to myocarditis and pericarditis after COVID-19 mRNA vaccination in the period May 15 to September 15, 2021. The setting was a multicenter study including all 18 Danish Pediatric Departments, providing 24 hours emergency service, and in- and out-patient treatment for all Danish inhabitants ≤ 17 years of age. As part of a pediatric nationwide COVID-19 research set-up, all 18 departments had a principal investigator responsible for prospective real-time data collection of vaccine-associated disease from May 15, 2021. Cases of myopericarditis were cross checked with the Danish VAERS to minimize the risk of missing cases. Due to unusual severity, case 12 has been reported previously.³

To calculate the incidence of myopericarditis associated with mRNA COVID-19 vaccination among Danish adolescents, the number of individuals 12–17 years of age who had received 1 dose of mRNA COVID-19 vaccine from May 15 to August 15, 2021, was attained from the National COVID-19-vaccine Database at the Statens Serum Institut.

The incidence of cardiac involvement due to SARS-CoV-2 infection in Danish adolescents 12–17 years of age was calculated

from our prospective nationwide study of multisystem inflammatory syndrome in children (MIS-C) in Denmark during the COVID-19 era (March 1, 2020, to 28 February 28, 2021).⁴ The background incidence of myocarditis in Danish adolescents 12–17 years of age was calculated using the Danish National Patient Register in 2014–2018, the pre-COVID-19 era.

Informed adolescent and parental consents were provided before participation. The study was approved by the Ethics Committee of Capital Region of Denmark (H-20028631) and the Danish Data Protection Agency (P-2019-29).

RESULTS

Thirteen (87%) male and 2 (13%) female previous healthy adolescents were hospitalized with myopericarditis after receiving Pfizer-BioNTech mRNA COVID-19 vaccination (Table 1). Twelve (80%) patients had myocarditis or myopericarditis (cases 1–12), including 1 meeting the criteria for MIS-C after vaccination (MIS-V) (case 12).³ Three (20%) had pericarditis (cases 13–15). Eight (53%) patients presented with chest pain after the first vaccine and 7 (47%) after the second vaccine. Eleven (73%) had fever. Investigations for differential diagnoses did not reveal viral or bacterial causes. The patients did not have previous SARS-CoV-2 infection, determined by history, repetitive PCR investigations, or negative nucleocapsid antibodies, except case 1 (confirmed by PCR 8 months before) and 8 (confirmed by nucleocapsid antibodies). All patients had resolution of symptoms with nonsteroidal anti-inflammatory drugs or no treatment, except case 12 who required treatment at intensive care unit. The median duration of hospitalization was 3 days (1–10).

A total of 133,477 males and 127,857 females 12–17 years of age had received the first vaccine between May 15 to August 15, 2021. The incidence of myopericarditis among males and females 12–17 years of age was 97 and 16 per million, equaling 1 of 10,000 males and 1 in 63,000 females, respectively.

During the first 12 months of the COVID-19 era, 6 males and 3 females 12–17 years of age with MIS-C and elevated troponin levels were identified among 16,900 males and 16,044 females 12–17 years of age infected with SARS-CoV-2. This equals 355 and 187 per million male and female adolescents infected with SARS-CoV-2 (1 in 2800 males and 1 in 5300 females), significantly higher than the incidence of myopericarditis after COVID-19 vaccination in both males and females (Fisher's exact test; $P < 0.01$). During the pre-COVID-19 era (2014–2018), the monthly incidence of myocarditis was 3 males and 0.5 females per million Danish males and females 12–17 years of age, respectively, equaling 12 males and 2 females per million during a corresponding 4-month period.

DISCUSSION

This study is based on a prospective detailed phenotyping of myopericarditis cases after Pfizer-BioNTech mRNA COVID vaccination in the very well registered population of Denmark. Among individuals 12–17 years of age, the study revealed an incidence of 97 males and 16 females per million. The incidence among males was higher than the reported rates until now from the US VAERS by Gargano et al finding 63 cases per million male adolescents 12–17 years of age.¹ Although that report was based on 8.9 million vaccinated adolescents, underreporting is one of the main limitations of this passive surveillance system.^{1,2}

The incidences in our study are encumbered with uncertainty due to the small population of Denmark. Further, our incidences may be overestimated due to possible inclusion of cases unrelated to the vaccine, but occurring in vaccinated adolescents, since myopericarditis without a known etiology is quite common among male adolescents.⁵ Such overestimation is expected to be similar in the reported rates from the US VAERS. We estimated

the background incidence of myocarditis to be 12 male and 2 female adolescents per million during a four-month period. Thus, the incidence of mRNA COVID-19 vaccine induced myopericarditis among adolescents is likely to be 10% lower than the reported incidences.

On the contrary, our incidences may also be underestimated. First, cases may have gone undiagnosed due to lack of clinical suspicion of this new association between vaccination and myopericarditis. Accordingly, 4 patients were initially discharged without evaluation for myocarditis despite chest pain and fever following COVID vaccination. Second, the inclusion period ended 4 weeks after the first vaccine. As myopericarditis appears to be more frequent after the second dose, cases could have been missed if the second dose was not administered timely. Finally, the incidences could be underestimated if patients were admitted to Departments of Adult Cardiology. Our research set-up included all Pediatric Departments in Denmark, but not Departments of Adult Cardiology, as the national guidelines recommend referral of adolescents with myopericarditis to the 3 Tertiary Pediatric Cardiology Centers in Denmark. Despite, 2 patients were admitted to Departments of Adult Cardiology and it cannot be excluded that other patients were admitted likewise, and not included in the study. However, this is less likely as the cross check with the Nationwide VAERS, as part of this study, did not reveal additional cases from Departments of Adult Cardiology.

Studies from the United States have found three-quarters, or more, to occur after the second vaccine.^{1,6} In contrast, our cases occurred equally after the first and the second vaccine. In 2 patients, myocarditis occurred 5 weeks after the first vaccine, just before the planned administration of the second vaccine, which was delayed according to the recommended dose interval of 3 weeks. Thus, we speculate that myocarditis may occur *several weeks* after the first vaccine, independent of the second dose, similar to the time interval between exposure of SARS-CoV-2 and the development of MIS-C. However, this hypothesis remains unexplored as most individuals receive the second vaccines after 3 weeks.

The mild phenotype of myopericarditis cases in our study were comparable with cases described in other studies,^{1,6} except 1 patient with myocarditis and MIS-C, who needed treatment at intensive care unit. This contrasts MIS-C with cardiac involvement following SARS-CoV-2 infection, where more than half of patients need treatment at intensive care unit.^{4,7} We found the incidence of MIS-C with cardiac involvement among SARS-CoV-2 infected adolescents significantly higher than myopericarditis after COVID-19 vaccination in both males and females (355 vs. 97 per million males and 187 vs. 16 per million females), although both estimates are encumbered with uncertainty due to the few cases included. Yet, these incidences may be difficult to compare, as most individuals are expected to receive the COVID-19 vaccination with a mass vaccination strategy, while the total number of adolescents who will become infected with SARS-CoV-2 may be low in countries with high vaccination coverage among the adult population.

In conclusion, this population-based prospective study suggests the incidence of myopericarditis in male adolescents to be higher than previous reported and that more severe phenotypes of myopericarditis may occur.

REFERENCES

1. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:977–982.
2. Blumenthal KG, Robinson LB, Camargo CA Jr, et al. Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA*. 2021;325:1562–1565.
3. Chai Q, Nygaard U, Schmidt R, et al. Multisystem inflammatory syndrome in a male adolescent after the second Pfizer-BioNTech SARS-CoV-2 vaccine

TABLE 1. Cases of Myopericarditis After mRNA COVID-19 Vaccination in Danish Adolescents

Disease	Gender	Age	mRNA Vaccine		SARS-CoV-2		Biochemistry*							ECHO	Cardiac MRI	Treatment	Hospital Admission Days
			Dose 1†	Dose 2‡	PCR‡	Nucleocapsid IgG	Spike IgG	CRP mg/L§	TnI/TnT ng/L¶	CK-MB µg/L	BNP pmol/L**	ECG					
													Days				
1 Myocarditis	♂	13	-24	-1	Negative	NE	NE	NE	1554	NE	Normal	Normal	T-wave inversion	Normal	Abnormal††	NSAID	3
2 Myocarditis	♂	14	-24	-2	Negative	Negative 0.3 AU/mL	Positive >3.500 AU/mL	21	NE/1640	68	Normal	Normal	Normal	Normal	Normal	NSAID	5
3 Myocarditis	♀	15	-39	%	Negative	NE	NE	20	7.920/364	Normal	Normal	Normal	Normal	Abnormal††	None	3	
4 Myocarditis	♀	16	-35	%	Negative	Negative 0.2 AU/mL	Positive 245 AU/mL	200	5.460/453	17	Normal	Normal	T-wave inversion	Normal	Abnormal††	None	3
5 Myocarditis	♂	15	-23	-2	Negative	Negative 0.4 AU/mL	Positive 841 AU/mL	Normal	162/21	Normal	Normal	Normal	Normal	Normal	Normal	None	3
6 Myocarditis	♂	16	-8	%	Negative	Negative 0.1 AU/mL	Positive 671 AU/mL	48	10/normal	Normal	NE	Normal	Normal	Normal	NE	None	5
7 Myocarditis	♂	17	-55	-27	NE	Negative 0.4 AU/mL	Positive >3.500 AU/mL	94	NE/1.860	Normal	130	Normal	T-wave inversion	Normal	Abnormal††	NSAID	3
8 Myocarditis	♂	17	-1	%	Negative	Negative 0.1 AU/mL	Positive 65 AU/mL	60	3.653/NE	12	Normal	Normal	Abnormal	Normal	Abnormal††	NSAID	4
9 Myocarditis	♂	17	-1	%	Negative	Positive 28 AU/mL	Positive 99 AU/mL	73	NE/363	30	Normal	Normal	Normal	Normal	Normal	NSAID	4
10 Myopericarditis	♂	16	-46	-3	NE	NE	NE	37	12.600/NE	26	154	NE	ST-elevation	LVEF 45%	Abnormal††	None	4
11 Myopericarditis	♂	17	-3	%	Negative	Negative 0.3 AU/mL	Positive 3 AU/mL	50	17.500/NE	NA	NE	NE	ST-elevation	LVEF 50%	NE	NSAID	5
12 Myocarditis /MIS-V	♂	17	-46	-5	Negative	Negative <1.1 AU/mL	Positive 5.680 IU/mL	305	10.507/219	69	17.844	Normal	Normal	Normal	Abnormal††	IVIG, steroid	10
13 Pericarditis	♂	16	-36	-1	NE	Negative 0.1 AU/mL	Positive 3.700 AU/mL	15	Normal	Normal	Normal	Normal	ST-elevation	Normal	NE	NSAID	2
14 Pericarditis	♂	17	-4	%	NE	NE	NE	Normal	Normal	Normal	NE	NE	ST-elevation	Pericardial effusion	NE	NSAID	1
15 Pericarditis	♂	17	-2	%	NE	NE	NE	Normal	Normal	Normal	NE	NE	ST-elevation	Normal	NE	NSAID	1

*Highest value.
 †Days from vaccination to initiation of chest pain.
 ‡SARS-CoV-2 PCR at admission.
 §Reference limit of CRP is 10 mg/L.
 ¶Reference limit of TnI and TnT is 5 ng/L and 14 ng/L.
 **Reference limit of CK-MB is 7 µg/L.
 ††Reference limit of BNP is 125 pmol/L.
 †††Six of 9 (67%) cases met the diagnostic cardiac MRI Lake Louise criteria for myocarditis.
 BNP indicates brain natriuretic peptide; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; MIS-V, multisystem inflammatory syndrome after vaccination; MRI, magnetic resonance imaging; NE, not examined; NSAID, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; Tn, Troponin.

- [published online ahead of print October 7, 2021]. *ACTA Paediatrica*. doi: 10.1111/apa.16141.
4. Holm M, Hartling UB, Schmidt LS, et al. Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus 2. *Acta Paediatr*. 2021;110:2581–2583.
 5. Arola A, Pikkarainen E, Sipilä JO, et al. Occurrence and features of childhood myocarditis: a nationwide study in Finland. *J Am Heart Assoc*. 2017;6:e005306.
 6. Jain SS, Steele JM, Fonseca B, et al. COVID-19 vaccination-associated myocarditis in adolescents [published online ahead of print August 13, 2021]. *Pediatrics*. doi: 10.1542/peds.2021-053427
 7. Feldstein LR, Tenforde MW, Friedman KG, et al.; Overcoming COVID-19 Investigators. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. *JAMA*. 2021;325:1074–1087.