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Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination

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Background. Age-specific incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination in Asia is lacking. This study aimed to study the clinical characteristics and incidence of acute myocarditis/pericarditis among Hong Kong adolescents following Comirnaty vaccination.

Methods. This is a population cohort study in Hong Kong that monitored adverse events following immunization through a pharmacovigilance system for coronavirus disease 2019 (COVID-19) vaccines. All adolescents aged between 12 and 17 years following Comirnaty vaccination were monitored under the COVID-19 vaccine adverse event response and evaluation program. The clinical characteristics and overall incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination were analyzed.

Results. Between 14 June 2021 and 4 September 2021, 33 Chinese adolescents who developed acute myocarditis/pericarditis following Comirnaty vaccination were identified. In total, 29 (87.88%) were male and 4 (12.12%) were female, with a median age of 15.25 years. And 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis/pericarditis after receiving the second and first dose, respectively. All cases are mild and required only conservative management. The overall incidence of acute myocarditis/pericarditis was 18.52 (95% confidence interval [CI], 11.67–29.01) per 100 000 persons vaccinated. The incidence after the first and second doses were 3.37 (95% CI, 1.12–9.51) and 21.22 (95% CI, 13.78–32.28 per 100 000 persons vaccinated, respectively. Among male adolescents, the incidence after the first and second doses were 5.57 (95% CI, 2.38–12.53) and 37.32 (95% CI, 26.98–51.25) per 100 000 persons vaccinated.

Conclusions. There is a significant increase in the risk of acute myocarditis/pericarditis following Comirnaty vaccination among Chinese male adolescents, especially after the second dose.

Keywords. myocarditis; pericarditis; adolescents; Comirnaty; Hong Kong.

The coronavirus disease 2019 (COVID-19) infection in children is generally mild, but serious complications, such as pediatric multisystem inflammatory syndrome—temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS), can occur [1]. Prolonged social distancing policies have also led to significant psychosocial impacts on children and their families in the community [2]. Enormous efforts have been made to control the spread of the virus through universal vaccination to achieve herd immunity to return us to a semblance of normality.

Currently, the vaccination program of the Hong Kong Government has authorized 2 COVID-19 vaccines: the CoronaVac from Sinovac Biotech (Hong Kong) Limited and Comirnaty vaccine (BNT162b2) from Fosun-BioNTech. On 14 June 2021, the government of the Hong Kong Special Administrative Region (HKSAR) commenced vaccination of the Comirnaty vaccine (BNT162b2) from Fosun-BioNTech

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to adolescents by lowering of the age limit from 16 to 12 years after reviewing the available evidence by the advisory panel on COVID-19 Vaccines of the Food and Health Bureau, HKSAR Government [3]. The drug office of the Department of Health (DH), the drug regulatory authority in Hong Kong, has implemented a pharmacovigilance system for COVID-19 vaccines that monitors reports of adverse events following immunization (AEFI). The COVID-19 vaccine Adverse event Response and Evaluation (CARE) program was set up, an active surveillance system, to evaluate AEFI data from the general population using electronic medical records from Hospital Authority and vaccination records from the DH. The CARE program actively identifies AEFI and conduct epidemiological study to evaluate the association between vaccinations and subsequent adverse event [4, 5].

The Comirnaty is a messenger RNA (mRNA) vaccine that is highly effective in preventing hospitalizations and deaths due to COVID-19 [6]. Although Comirnaty has a favorable safety profile, various regulatory agencies have advocated continuous monitoring of its safety, as rare and long-term adverse reactions might not have been detected in the clinical trials and early post-marketing reports [7]. Recently, there have been emerging case reports of acute myocarditis following mRNA COVID-19 vaccination in healthy young adolescent and adult males [8–10]. The United Kingdom has only approved offering 1 dose of the Pfizer-BioNTech vaccine to healthy adolescents aged 12–15 years old so far, instead of giving the recommended 2 doses [11]. Yet an in-depth population-based investigation of the age-specific incidence of acute myocarditis/pericarditis following mRNA COVID-19 vaccination in Asian adolescents is lacking. This study aims to report the clinical characteristics and estimate the incidence of acute myocarditis following vaccination with Comirnaty in adolescents in Hong Kong.

METHODS

This was a population cohort study aimed at identifying all suspected cases of acute myocarditis in adolescents aged between 12 and 17 years who received the Comirnaty vaccine between 14 June 2021 and 4 September 2021. All individuals receiving the Comirnaty vaccine have also consented to their vaccination records being linked to their corresponding comprehensive electronic health records held by the Hospital Authority (HA), the major publicly funded healthcare provider, through the CARE program [4]. All suspected cases of acute myocarditis/pericarditis that occur within 14 days after receiving either the first or the second dose of the Comirnaty vaccine and admitted to one of the HA hospitals are reported to the Advanced Incident Reporting System (AIRS) on admission, a system for HA to report adverse drug events and AEFI to DH.

Suspected cases of acute myocarditis/pericarditis who received Comirnaty vaccines during the study period were investigated according to the Hong Kong Pediatric Investigation Protocol for Comirnaty-related Myocarditis/Pericarditis (Supplementary file 1), which was implemented in all HA hospitals. Demographics including date of birth, sex, ethnicity, date of receiving the first and the second dose of COVID-19 vaccines, symptoms, date of onset, and past medical histories were reviewed. Microbiological investigations including nasopharyngeal swab (NPS) for SARS-CoV-2 and common respiratory viruses including influenza A/B/C, parainfluenza virus 1/2/3/4, adenovirus, human metapneumovirus, and respiratory syncytial virus, and throat and rectal swabs for enteroviruses were tested. SARS-CoV-2 anti-receptor binding domain (RBD) and anti-nucleocapsid protein (NP) antibodies were tested to differentiate whether the patients had a history of COVID-19 infection. Cardiac enzymes, including high-sensitivity troponin I (hsTnI), high-sensitivity troponin T (hsTnT or TnT), electrocardiogram (ECG), and echocardiogram were serially monitored. ECGs were interpreted by 1 single investigator (S. S. T.). Echocardiograms were performed and interpreted by the cardiologists of each admitting hospital. Cardiac magnetic resonance imaging (cMRI) was performed within two weeks of symptoms onset either at the admission hospital, or referred to the Hong Kong Children's Hospital if no slots were immediately available. The cMRI images were interpreted by the radiologists of each magnetic resonance imaging (MRI) unit. The study team followed the myocarditis and pericarditis case definitions created by the Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Working Group [12].

Estimation of Incidence and Statistical Analysis

Vaccination records within the study period were extracted from the DH in Hong Kong since the commencement of mass COVID-19 vaccinations in adolescents aged 12–17 years on 14 June 2021 to 4 September 2021. The cutoff date for follow-up time was 18 September 2021, allowing for all participants to have a 14-day follow-up period. De-identified electronic health records were retrieved from the HA Clinical Data Analysis and Reporting System (CDARS), which has been successfully used in a previous COVID-19 vaccine-related pharmacovigilance study [4]. Subjects with a history of primary myocarditis/pericarditis prior to the study period were excluded. Cases of acute myocarditis/pericarditis following Comirnaty vaccination were identified if they occurred within 14 days of either the first or the second vaccine dose. We estimated the background rate of acute myocarditis/pericarditis, cases of the first primary diagnosis were extracted from CDARS from 2011 to 2020 using data available from 14 June to 4 September of each year. For each year, those with a history of acute myocarditis/pericarditis in the prior year to the study period were censored.

Separated cases related to the first dose or to the second dose were also calculated. Acute myocarditis/pericarditis related to

the first dose was defined as the first cases within 14 days of the first dose. Acute myocarditis/pericarditis related to the second dose was defined as the first cases within 14 days of the second dose. The 14 days was the upper end of the reporting of myocarditis/pericarditis cases following vaccination according to the DH and HA reporting policies. The incidence of clinically confirmed myocarditis/pericarditis per 100 000 doses administered as well as number of cases per 100 000 doses for first dose and second dose were estimated. We calculated 95% confidence intervals (CI) for all incidences calculated using Poisson distribution. The incidence rate of acute myocarditis/pericarditis associated with the Comirnaty vaccine was compared with the background incidence rate of acute myocarditis/pericarditis in 2020 using 100 000 doses per 14-days. Sensitivity analyses were conducted using (1) the background incidence rate in 2018 and 2019 and the average background incidence rate from 2011 to 2020 using 100 000 doses per 14 days and (2) changed the incidence using doses per 28 days. Subgroup analysis was conducted by sex. Some comparisons to background years were not possible as there were zero cases of myocarditis/pericarditis recorded in background years. Median and interquartile ranges (IQR) were used to describe skewed data. All statistical tests were 2-sided, and *P*-values at a level of 5% were considered statistically significant. Statistical analyses were conducted using R version 4.0.3 (www.R-project.org). For quality assurance, 2 investigators (E. C. C. and R. D. S.) independently conducted the statistical analyses.

Ethical Approval

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW21-149 and UW21-138) and the Department of Health Ethics Committee (LM21/2021).

RESULTS

Between 14 June and 4 September 2021, a total of 33 cases of myocarditis/pericarditis within 14 days following vaccination with Comirnaty were identified. Twenty-five (75.76%) were definite, 7 (21.21%) were probable, and 1 (3.03%) were possible cases (Table 1). The patients were all Chinese adolescents with no history of cardiac diseases; 29 (87.88%) were male and 4 (12.12%) were female, with a median age of 15.25 years. In total, 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis/pericarditis after receiving the second and first dose, respectively. These patients developed myocarditis/pericarditis at a median of 2 days after receiving the last dose of the vaccine. All of them presented with chest pain. Three cases (9.09%) had normal troponin levels, 2 of them were cases of definite pericarditis and 1 had possible myocarditis. Six (18.18%) had normal ECGs, 25 (75.76%) had normal echocardiograms, and 7 (21.88%) had normal cMRI. None had significant arrhythmias. All patients had no identifiable infections. They also had no current and past history of COVID-19 infection, as evidenced by a negative SARS-CoV-2 PCR on admission and the absent of anti-SARS-CoV-2 NP antibodies in their serum. All patients had mild diseases requiring no treatment or symptomatic relief by nonsteroidal anti-inflammatory drugs (NSAIDs). They spontaneously recovered without the need of systemic steroids, intravenous immunoglobulins, or inotropic or circulatory support.

There have been 305 406 doses of Comirnaty vaccine administered to 178 163 individuals aged 12–17 years (88 357 [49.59%] are female) since the commencement of the vaccination program on 14 June 2021 until 4 September 2021. This represented 51.84% of the population between 12 and 17 years (178 163/343 700) in Hong Kong in mid-2021 [13]. The overall incidence for acute myocarditis/pericarditis was 18.52 (95% CI, 11.67–29.09) per 100 000 persons. The incidence after the first and second doses were 3.37 (95% CI, 1.12–9.51) and 21.22 (95% CI, 13.78–32.28) per 100 000 persons vaccinated, respectively (Table 2). Incidence was higher among male adolescents compared to females (Table 2). Incidence rates compared with previous years' background rates are shown in Table 2 and Supplementary Tables 1–3. Compared to the background incidence rate of acute myocarditis/pericarditis in 2020 there were significantly higher incidence rate differences in those vaccinated (Table 2). Sensitivity analyses using the background incidence rate in 2018, 2019, and 2020 and the average background incidence rate from 2011 to 2020 using per 100 000 per 28-days also demonstrated significantly higher incidence rate differences in those vaccinated which was consistent with the main results (Supplementary Tables 4–8).

Among males after their first dose, there was a significantly higher incidence rate difference compared the background rate in 2020. After the second dose there was significantly higher incidence rate difference between the background rate in 2020 and all participants and males (Table 3).

DISCUSSION

To our best knowledge, this is the first study in adolescents using data from the territory-wide post-COVID-19 vaccination monitoring system to analyze the incidence of acute myocarditis/pericarditis associated with the Comirnaty vaccine for adolescents in Asia.

Our analysis revealed that the overall incidence of acute myocarditis/pericarditis in adolescent following the Comirnaty vaccination was 18.52 per 100 000 persons vaccinated. Majority cases involved healthy adolescent males after receiving the second dose. No other infective causes including SARS-CoV-2 infection were identified. Conservative management with NSAIDs was sufficient. This higher

Table 1. Clinical Characteristics of Adolescents With Myocarditis/Pericarditis Following Comirnaty Vaccination in Hong Kong

No.	Sex/Age at Presentation (years)	Present After First or Second Dose	No. of Days After Receiving the Last Dose	Symptoms	Peak Troponin Levels(hsTnT/ hsTnI/TnT) (ng/L)[b]	Most Significant ECG Changes	ECHO	MRI Findings	Final Diagnosis (Level of Certainty[a])
1	M/15.66	Second	2	Chest pain, headache	TnT 793 hsTnI 2506 (elevated)	STE in II, III, aVF, V3-V5	Normal	Patchy edema; diffuse EGE; patchy pericardial and subepicardial LGE; normal ECV	Perimyocarditis (Definite)
2	M/14.52	Second	1	Chest pain, fever	TnT 646 hsTnI 6342 (elevated)	TWI and biphasic T waves in III, aVF, V4-V6	Normal	Borderline LV function; elevated T1 and T2 mapping values and ECV; presence of LGE	Myocarditis (Definite)
3	M/13.53	Second	2	Dizziness, SOB, chest pain	TnT 1749 (elevated)	STE in V2-V6TWI in aVL; biphasic Ts in V3–V4	Normal	Elevated T1 and T2 mapping values and ECV; pericardium and subepicardial muscles LGE and T2 hyperintensity	Perimyocarditis (Definite)
4	M/13.05	First	2	Chest pain	TnT 302 (elevated)	STE in V3–V6; TWI in III; STD in aVR	Normal	Elevated T1 and T2 mapping values and ECV; pericardial LGE extending to subepicardial region	Perimyocarditis (Definite)
5	M/14.34	Second	1	Chest pain	TnT 993 (elevated)	STE in V3–V5; TWI in I, aVL; biphasic T waves in V3–V6	Normal	Borderline LV function; subepicardial LGE; elevated T1 and T2 mapping values and ECV; hyperintense pericardium	Perimyocarditis (Definite)
6	M/16.99	Second	3	Chest pain	TnT 948 (elevated)	STE in V2–V6	Mildly impaired LV global longitudinal strain	Borderline LV function, small pericardial effusion; elevated ECV, T1 and T2 mapping values; patchy LGE	Perimyocarditis (Definite)
7	M/15.22	Second	2	Chest pain	hsTnI 11415 (elevated)	Normal	Normal	Elevated T1 and T2 mapping values; presence of patchy EGE; normal ECV; subepicardial LGE	Myocarditis (Definite)
8	M/15.32	Second	2	Chest pain, fever	hsTnI 16806 (elevated)	STD and TWI in V1–2; STE in lead II, III, aVF; ST/T wave abnormality in II, III, aVF, V4–V6	Borderline LV function (LVFS 28%), minimal pericardial effusion	Mild increase STIR signal; faint patchy LGE; trace pericardial effusion	Perimyocarditis (Definite)
9	M/17.14	First	1	Chest pain	hsTnI 19110 (elevated)	STE in II, III, aVF, V4–V6	Tiny rim of pericardial effusion	Elevated T1 and T2 mapping values and ECV; no definite EGE; LGE present; patchy pericardial enhancement	Perimyocarditis (Definite)
10	F/14.07	Second	3	Chest discomfort, transient SOB	hsTnI 54.9 (elevated)	STE in V4–V5	Normal	Elevated T1 and T2 mapping values and ECV; LGE and pericardial enhancement	Perimyocarditis (Definite)
11	M/13.75	Second	2	Chest pain, palpitation, fever	hsTnI 6254 (elevated)	Sinus tach; STE in II, III, aVF, V3–V5	Normal	Elevated T1 and T2 mapping values and ECV; presence of LGE	Myocarditis (Definite)
12	M/12.74	Second	1	Chest pain, palpitations, dizziness	hsTnI 14766 (elevated)	STD in aVR and V1; STE I-III, aVF, V4–V6	Thin rim of pericardial effusion, hyperechoic pericardium	Elevated T1 mapping value; presence of myocardial edema with increased T2W signal	Perimyocarditis (Definite)
13	F/12.97	Second	1	Chest pain, fever, headache, palpitations, subjective SOB	hsTnI 2309 (elevated)	Normal	Normal	Elevated T1 and T2 mapping values and ECV; pericardial and subepicardial LGE; small pericardial effusion	Perimyocarditis (Definite)
14	M/17.85	Second	3	Chest pain	hsTnI 30267 (elevated)	STE in I, II, aVF, V4–V6, STD in aVR, V1-V2; TWI in III; biphasic Ts in V3–V5	Borderline contractility	Elevated T1 and T2 mapping values and ECV; subepicardial and mid-wall LGE; small pericardial effusion	Perimyocarditis (Definite)

Table 1. Continued

No.	Sex/Age at Presentation (years)	Present After First or Second Dose	No. of Days After Receiving the Last Dose	Symptoms	Peak Troponin Levels(hsTnT/ hsTnI/TnT) (ng/L)[b]	Most Significant ECG Changes	ECHO	MRI Findings	Final Diagnosis (Level of Certainty[a])
15	M/14.99	Second	1	Fever, chest pain, palpitation, SOB, dizziness	TnT 323 (elevated)	STE in V3-5TWI in aVR and V1	Normal	T2W hyperintensity within myocardium; regional LGE; 5mm pericardial effusion	Perimyocarditis (Definite)
16	M/16.88	Second	4	Chest pain, SOB	hsTnT < 14 (normal)	STE in V2 and V4	Increased echogenicity over LV free wall	Not done	Pericarditis (Definite)
17	M/17.33	Second	2	Chest pain, fever, palpitation	hsTnI 767 (elevated)	STE in II, III, aVF, V3–V6	Normal	T2W hyperintense myocardial edema at mid and apex of LV	Myocarditis (Definite)
18	M/14.25	First	3	Chest pain, fever	hsTnI 184 (elevated)	STD in II, III, aVF	Normal	T2W hyperintense myocardial edema at basal lateral and basal septal segments of LV	Myocarditis (Definite)
19	M/15.95	Second	2	Chest discomfort, palpitation	hsTnI 3561 (elevated)	STE in II, aVF, V4-V6	Normal	T2W hyperintense myocardial edema with LGE at apical lateral segment and subepicardial region	Myocarditis (Definite)
20	M/14.17	Second	2	Chest pain	TnT 1058 (elevated)	STE in V4–V6; TWI in III, aVF	Normal	Mild T2W hyperintense signals and increased T2 mapping value at inferolateral LV wall	Myocarditis (Definite)
21	M/15.70	Second	2	Chest pain	hsTnI 263 (elevated)	STE II, III, aVF, V4–V6	Normal	Mild subepicardial basal to mid-ventricular lateral wall LGE and elevated T1 mapping value	Myocarditis (Definite)
22	M/15.65	Second	1	Chest pain, palpitations	hsTnI 2210 TnT 283 (elevated)	STE V2–V6	Normal	Generalized myocardial hyperintensity in TIRM sequence; presence of hyperemia; subepicardial LGE; small pericardial effusion	Perimyocarditis (Definite)
23	F/16.89	First	2	Palpitation, near syncope, nausea, vomiting	hsTnT 30 (elevated)	Normal	Normal	LV myocardium diffuse increased T2 signal; patchy early Gd enhancement	Myocarditis (Definite)
24	M/16.88	Second	2	Chest pain, headache, dizziness	TnT 669 (elevated)	Normal	Borderline LV function(LVFS 29.1%)	Normal	Myocarditis (Definite)
25	M/14.78	Second	2	Chest pain, palpitation	hsTnT < 14 (normal)	STE in I,II, V2–V6, and STD in aVR	Prominent pericardial echogenicity	Normal	Pericarditis (Definite)
26	M/14.18	First	2	Chest pain	hsTnI 513 (elevated)	Normal	Normal	Equivocal myocardial edema due to motion artefacts	Myocarditis (Probable)
27	F/15.25	Second	6	Chest pain	hsTnI 77 (elevated)	STE V2–V3; biphasic Ts in V3	Normal	Normal	Myocarditis (Probable)
28	M/14.31	Second	14	Chest discomfort, transient SOB, headache, dizziness	hsTnI 201 (elevated)	TWI and ST depression in II, III, aVF; biphasic Ts in V3–V5	Normal	Normal	Myocarditis (Probable)
29	M/17.87	First	2	Chest pain	hsTnI 29.2 (elevated)	STE in II, V3–V6	Normal	Normal	Myocarditis (Probable)
30	M/17.64	Second	2	Chest pain, fever, headache	hsTnI 4874 (elevated)	STE in V2–V6, TWI in aVF/III; biphasic Ts in II, aVF, V4–V6	Normal	Normal	Myocarditis (Probable)

Table 1. Continued

No.	Sex/Age at Presentation (years)	Present After First or Second Dose	No. of Days After Receiving the Last Dose	Symptoms	Peak Troponin Levels(hsTnT/ hsTnI/TnT) (ng/L)[b]	Most Significant ECG Changes	ECHO	MRI Findings	Final Diagnosis (Level of Certainty[a])
31	M/12.85	Second	2	Chest pain, vomiting, SOB	hsTnT 39	Sinus tachycardia; STE in II, III, aVF; V2–V6	Normal	Global hyperintensity in myocardium in T2W images with hyperintensity in early post-Gd images but no LGE. Suspicious of myocarditis	Myocarditis (Probable)
32	M/15.79	Second	10	Chest pain, dizziness, near syncope	hsTnT 25 (elevated)	Normal	Normal	Normal	Myocarditis (Probable)
33	M/16.76	Second	2	Fever, chest discomfort, palpitation, transient SOB	hsTnT < 14 (normal)	STE in V2–V6	Normal	Normal	Myocarditis (Possible—elevated CRP)
34[c]	M/15.07	Second	25	Chest pain	TnT 269 hsTnI 3850	STE in V2–V6	Mild pericardial and LV free wall echogenicity	Not done	Perimyocarditis (Definite)
35[c]	F/12.78	Second	26	Vomiting, palpitation, reduced exercise tolerance	hsTnI 566	STE in II, V2–V5; STD in aVR; TWI in aVL; Q waves in I and aVL	Hyperechoic pericardium	Elevated T1 mapping values; subepicardial LGE	Perimyocarditis (Definite)

Abbreviations: CRP, C reactive protein; ECG, electrocardiogram; ECHO, echocardiogram; ECV, extracellular volume; EGE, early gadolinium enhancement; Gd, gadolinium; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; LGE, late gadolinium enhancement; LV, left ventricle; LVFS, left ventricle fractional shortening; MRI, magnetic resonance imaging; SOB, shortness of breath; STD, ST depression; STE, ST elevation; STIR, short tau inversion recovery; T2W, T2-weighted; TWI, T wave inversion; TnT, troponin T.

[a]Brighton Collaboration Myocarditis Case Definition Level of Certainty (LOC) Classification.

[b]Elevated troponin level based on reference values provided by each laboratory. Subjects with two different troponin measures were because of transferal to another hospital.

[c]Cases 34 and 35 presented > 14 days after receiving the second doses, therefore they were only included in the sensitivity analyses (Supplementary Tables 4–8).

Table 2. Incidence Rate Differences of Myocarditis/Pericarditis Cases Following Comirnaty Vaccination Stratified by Sex and Compared to Background Rate in 2020

	Incidence Rate (per 100 000 person-14 days, 95% CI)	Background Incidence Rate in 2020[a] (per 100 000 person-14 days, 95% CI)	Incidence Rate Difference (per 100 000 person-14 days, 95% CI)
Comirnaty			
Total	18.52 (11.67–29.01)	0.11 (.01–20.36)	**18.41 (9.95–26.87)**
Male	32.29 (22.78–45.4)	0.21 (.01–10.34)	**32.08 (20.91–43.25)**
Female	4.53 (1.76–11.11)	0	-

Values in bold represent a statistically significant difference ($P < .05$).

Abbreviation: CI, confidence interval.

[a]The background incidence rates were calculated using the reporting period (14 June to 4 September) in 2020 and truncated to incidence rate per 14 days.

incidence of myocarditis/pericarditis following Comirnaty vaccination than other jurisdictions is likely related to the heightened vigilance of healthcare professionals and the public [14], as well as the highly efficient CARE program for the monitoring and reporting of AEFI across Hong Kong [10]. Our pharmacovigilance system was able to capture mild cases of acute myocarditis/pericarditis and reveal the real-world incidence of acute myocarditis/pericarditis following the Comirnaty vaccination. Because the Pfizer-BioNTech vaccine was approved for large-scale immunization in many countries, there has been a higher observed risk of acute myocarditis/pericarditis among younger males receiving this vaccine [15]. The first reports in Israel were of 5 young males who developed mild myocarditis following vaccination with the BioNTech mRNA COVID-19 vaccine [16]. Subsequently, 23 US military males reported developing myocarditis after administering more than 2.8 million doses of either the Moderna or BioNTech mRNA COVID-19 vaccines to military personnel [9]. In children, so far, only 1 case series reported myocarditis following vaccinations with mRNA COVID-19 vaccines. These 7 cases were males aged 14–19 years who presented with transient mild symptoms, elevated troponin, and MRI changes suggestive of acute myocarditis or perimyocarditis. They were treated with NSAIDs, steroids, or intravenous immunoglobulin [8]. So far, all adults and adolescents with myocarditis/pericarditis following COVID-19 vaccinations, including those reported in the current study, have been mild cases [17]. However, the pathophysiology of acute myocarditis/pericarditis following the mRNA COVID-19 vaccine is still unclear, and the observation that only mRNA-based COVID-19 vaccines are associated with acute myocarditis remains unexplained. The causal association between mRNA vaccine and myopericarditis has recently been suggested in a mouse model. Higher systemic levels of mRNA lipid nanoparticles due to inadvertent intravenous injection or rapid return from the lymphatic circulation was proposed to increase this risk [18]. Further studies to delineate the pathophysiology of acute myocarditis/pericarditis associated with mRNA-based COVID-19 vaccines is urgently needed.

The US Center for Disease Control and Prevention (CDC) reported that the expected rates of myocarditis/pericarditis following the Comirnaty vaccination would be the highest among males aged between 12 and 29 years old, estimating 40.6 per million second doses administered [10]. The incidence rate of myocarditis/pericarditis following the Comirnaty vaccination in Hong Kong was much higher than those reported from the United States [10, 19]. However, it is important to note that the risk of myocardial injury in healthy young individuals including athletes following

Table 3. Incidence Rate Differences of Myocarditis/Pericarditis Cases Following the First and Second Doses of Comirnaty Vaccination Stratified by Sex and Compared to Background Rate in 2020

	Incidence Rate (per 100,000 person-14 days, 95% CI)	Background Incidence Rate in 2020[a] (per 100 000 person-14 days, 95% CI)	Incidence Rate Difference (per 100 000 person-14 days, 95% CI)
First dose of Comirnaty			
Total	3.37 (1.12–9.51)	0.11 (.01–20.36)	3.26 (−0.40 to 6.92)
Male	5.57 (2.38–12.53)	0.21 (.01—10.34)	**5.36 (0.65–10.07)**
Females	1.13 (0.16–6.58)	0	-
Second dose of Comirnaty			
Total	21.22 (13.78–32.28)	0.11 (.01–20.36)	**21.11 (12.06–30.16)**
Male	37.32 (26.98–51.25)	0.21 (.01–10.34)	**37.11 (25.10–49.12)**
Female	4.77 (1.90–11.44)	0	-

Values in bold represent a statistically significant difference ($P < .05$).

Abbreviation: CI, confidence interval.

[a]The background incidence rates were calculated using the reporting period (14 June to 4 September) in 2020 and truncated to incidence rate per 14 days.

COVID-19 infection is also considerably high [20], ranging from asymptomatic cases with abnormal cMRI only to fulminant myocarditis due to COVID-19 [21, 22]. Preliminary data in Israel demonstrated a 51% effectiveness after receiving 1 dose Pfizer-BioNTech vaccine among older adults [23]. As there have been essentially no local transmission of SARS-CoV-2 in Hong Kong since May 2021 [24], balancing the risk of acute myocarditis/pericarditis after receiving the second dose and the benefit of vaccination to protect complications related to COVID-19 infection, the Scientific Committee on Vaccine Preventable Diseases and the Scientific Committee on Emerging and Zoonotic Diseases under the Centre for Health Protection of the Department of Health of Hong Kong recommended adolescents between 12 and 17 years to receive 1 dose of the Comirnaty vaccine, instead of 2 doses, on 15 September 2021 [25]. Although our study provided the most comprehensive epidemiology of myocarditis/pericarditis following Comirnaty vaccination before the policy change, ongoing observations on the incidence of myocarditis/pericarditis following the Comirnaty vaccination with 1-dose Comirnaty vaccination as well as the rate of COVID-19 infections among adolescents in Hong Kong shall be conducted to provide real-world evidence on the risk and benefit of the policy change.

This study has several strengths and limitations. All subjects presented to the accident and emergency department or in the outpatient clinics in the public system received comprehensive reviews and investigations to rule out the possibility of myocarditis/pericarditis because of viral infection, and cMRI to confirm subtle inflammation of the myocardium. However, asymptomatic subjects and subjects with transient and subtle symptoms of acute myocarditis/pericarditis, such as tachycardia and mild chest discomfort, might not seek medical consultation or have sought medical consultation in the private sector which were not reported. Some patients had negative MRI results because not all MRI suites in Hong Kong's public hospitals have the capability for T1 and T2 mapping to calculate the extracellular volume, leading to lower sensitivities and unable to meet the 2018 Lake Louise Criteria for the diagnosis of myocarditis. Furthermore, the incidence of acute myocarditis/pericarditis following the COVID-19 vaccination remained to be high, possibly attributed to increased awareness of possible acute myocarditis/pericarditis following vaccination with COVID-19 vaccines compared with other jurisdictions, as well as to the CARE program to capture AEFI. The high incidence of acute myocarditis/pericarditis following Comirnaty vaccination among adolescents presented in this study is representable as the HA receives majority of emergency admissions in Hong Kong [4]. Finally, different criteria were likely used by clinicians in generating a diagnostic code among the nonvaccinated individuals for the calculation of the background myocarditis/pericarditis incidence as it was in a nonresearch setting. Nevertheless, we have included myocarditis and pericarditis of all causes, including idiopathic cases, for the calculation of the background incidence.

Conclusion

Chinese adolescent males have a higher risk of acute myocarditis/pericarditis following vaccination with Comirnaty, especially after the second dose. Medical professionals and recipients of the Comirnaty vaccine should be vigilant regarding the symptoms of acute myocarditis/pericarditis. Observations on the incidence of myocarditis/pericarditis following the Comirnaty vaccination after changing to 1-dose vaccination as well as the rate of COVID-19 infections among adolescents shall be conducted.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. I. and I. W. assessed and verified the data.

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Relations Committee for Society of Cardiovascular Computed Tomography. G. C. F. C. is the CMO of Xellera and advisor of Pangenia. Y. L. L. received Government funding for COVID-19 Vaccinations in Adolescents (COVA) and is the Chairman of the Scientific Committee on Vaccine Preventable Diseases, Centre for Health Protection, HKSAR. I. W. has received research funding outside of the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, Hong Kong Research Grants Council, Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, and National Health and Medical Research Council in Australia (Research grants on pharmacoepidemiology to The University of Hong Kong outside of the submitted work); consultancy fee for advising IQVIA on pharmacoepidemiology studies outside of the submitted work; payment for expert testimony from Appeal Court in Hong Kong (expert report on effects of cannabis outside of the submitted work); and speaker fees from Janssen and Medicine in the previous 3 years; reports the following leadership roles: Member of Pharmacy and Poisons Board (this is the regulatory agency in pharmaceutical product licensing), Member of the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization (advise the Hong Kong Government on safety of COVID-19 vaccines), and Member of the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government (advise the Hong Kong Government on the emergency use of COVID-19 vaccines). He is also an independent nonexecutive director of Jacobson Medical in Hong Kong (salaried). P. I. has received grants outside of the submitted work from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grants Council, and Hong Kong Jockey Club Charities Trust. M. T. Y. L. reports receiving Honorarium for a talk on ADHD. W. K. C. N. reports personal honoraria for Guerbet online lecture on pediatric cardiac imaging; holds 100 shares in Moderna stock, 50 shares in Biotech stock since April, owned 100 shares in Pfizer stock from July 2020 to January 2021. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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