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

Gilbert T. Chua, 1-3 Mike Yat Wah Kwan, 3-4 Celine S. L. Chui, 5-6 Robert David Smith, 4 Edmund Chi-Lok Cheung, 7 Tian Ma, 6 Miriam T. Y. Leung, 6 Sabrina Siu Ling Tsao, 8 Elaine Kan, 3 Wing Kei Carol Ng, 9 Victor Chi Man Chan, 10 Shuk Mui Tai, 10 Tak Chung Yu, 10 Kwok Piu Lee, 3 Joshua Sung Chih Wong, 3 Ying Kit Lin, 3 Chi Chiu Shek, 3 Agnes Sze Yin Leung, 10 Chit Kwong Chow, 11 Ka Wah Li, 12 Johnny Ma, 13 Wai Yuk Fung, 11 Daniel Lee, 11 Ming Yen Ng, 14 Wilfred Hsing Wong Wong, 1 Hing Wai Tsang, 1 Janette Kwok, 5 Daniel Leung, 1 Kin Lai Chung, 3 Chun Bong Chow, 3 Godfrey Chi Fung Chan, 12 Wing Hang Leung, 15 Kelvin Kai Wang To, 20 Kwok Yung Yuen, 7 Yu Lung Lou, 3 Ian Chi Kei Wong, 12, 21 and Patrick Ip 1

1Department of Pediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; 2Department of Paediatrics, Hong Kong Children's Hospital, Hong Kong SAR, China; 3Department of Pediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong SAR, China; 4School of Nursing, The University of Hong Kong, Hong Kong SAR, China; 5School of Public Health, The University of Hong Kong, Hong Kong SAR, China; 6Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong SAR, China; 7Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China; 8Department of Radiology, Hong Kong Children's Hospital, Hong Kong SAR, China; 9Department of Paediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China; 10Department of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China; 11Department of Paediatrics and Adolescent Medicine, United Christian Hospital, Hong Kong SAR, China; 12Department of Pediatrics and Adolescent Medicine, Tuen Mun Hospital, Hong Kong SAR, China; 13Department of Radiology, Caritas Medical Centre, Hong Kong SAR, China; 14Department of Radiology, North Llandau Hospital, Hong Kong SAR, China; 15Department of Radiology, Princess Margaret Hospital, Hong Kong SAR, China; 16Department of Radiology, Yan Chai Hospital, Hong Kong SAR, China; 17Department of Radiology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China; 18Department of Diagnostic Radiology, The University of Hong Kong, China; 19Department of Medical Imaging, The University of Hong Kong-Shenzhen Hospital, China; 20Division of Transplantation and Immunogenetics, Department of Pathology, Queen Mary Hospital, Hong Kong SAR, China; 21Quality and Safety Division, Hospital Authority Head office, Hong Kong SAR, China; 22Department of Microbiology, Carol Yu Centre for Infection, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; and 23Research Department of Practice and Policy, UCL School of Pharmacy, University College, London, United Kingdom.

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 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 per 100,000 persons vaccinated.

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 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—temporarily 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,
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 two-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
| 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) | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty) |
|-----|-----------------------------|---------------------------------|----------------------------------------|----------|---------------------------------------------|-----------------------------|------|--------------|-----------------------------------|
| 1   | M/15.66                    | Second                          | 2                                      | Chest pain, headache | TnT 793
hsTnI 2506 (elevated) | STE in II, III, aVF, V3-V5 | Normal | Patch 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/13.06                    | First                           | 2                                      | Chest pain | TnT 302 (elevated) | STE in V3-V6; TWI in II; 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/13.76                    | Second                          | 2                                      | Chest pain, palpitation, fever | hsTnI 6254 (elevated) | Sinus tach; STE in II, III, aVF; V3-V6 | Normal | Elevated T1 and T2 mapping values and ECV; presence of LGE | Myocarditis (Definite) |
| 12  | M/12.71                    | Second                          | 1                                      | Chest pain, palpitations, dizziness | hsTnI 14766 (elevated) | STD in aVR and V1; STE III, aVF; V4-V6 | Normal | 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) |
| 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/hsTnTnT) (ng/L) | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty) |
|-----|--------------------------------|----------------------------------|------------------------------------------|----------|------------------------------------------|--------------------------------|------|-------------|-------------------------------------|
| 15  | M/14.99                        | Second                           | 1                                        | Fever, chest pain, palpitation, SOB, dizziness | hsTnT 323 (elevated)       | STE in V3–STI 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 | hsTnT 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 | hsTnT 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 | hsTnT 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 II, 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 | hsTnT 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 | hsTnT 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 II, V2–V6, and STD in aVR | Prominent pericardial echogenicity | Normal | Pericarditis (Definite)   |
| 26  | M/14.18                        | First                            | 2                                        | Chest pain | hsTnT 513 (elevated)       | Normal | Normal | Equivocal myocardial edema due to motion artefacts | Myocarditis (Probable) |
| 27  | F/15.25                        | Second                           | 6                                        | Chest pain | hsTnT 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 | hsTnT 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 | hsTnT 29.2 (elevated)       | STE in II, V3–V6 | Normal | Normal | Myocarditis (Probable) |
| 30  | M/17.64                        | Second                           | 2                                        | Chest pain, fever, headache | hsTnT 487 (elevated)       | STE in V2–V6, TWI in aVF/III, biphasic Ts in II, aVF, V4–V6 | Normal | Normal | Myocarditis (Probable) |
| 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/hsTn(TnT)) (ng/L)<sup>a</sup> | Most Significant ECG Changes | ECHO | MRI Findings | Final Diagnosis (Level of Certainty)<sup>a</sup> |
|-----|---------------------------------|-----------------------------------|------------------------------------------|---------|------------------------------------------------|---------------------------------|------|-------------|---------------------------------|
| 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) | STE in V2–V6 | 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 | Normal | Myocarditis (Possible—elevated CRP) |
| 34<sup>c</sup> | 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<sup>c</sup> | 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; hsTn(T), 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.

<sup>a</sup>Brighton Collaboration Myocarditis Case Definition Level of Certainty (LOC) Classification.

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

<sup>c</sup>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).
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 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 2020a (per 100 000 person-14 days, 95% CI) | Incidence Rate Difference (per 100 000 person-14 days, 95% CI) |
|---------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------|
| Comirnaty                                         |                                                                          |                                                                 |
| Total                                            | 18.52 (.1167–29.01)                                                    | 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.

*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.

---

**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 2020a (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.

*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 copyrighted 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.
Concept and design. M. K., Y. L. L., I. W., and P. I.
Acquisition of data. M. K., J. W., V. C., S. M. T., K. P. L., Y. K. L., C. C. S., S. T., E. K., J. M., D. L., J. K. K. T., G. C. H. W. T., A. L., M. Y. N., C. K. C., and K. W. L.
Statistical analysis. C. C., W. W., E. C., T. T. M., and R. S.
Interpretation of data. All authors.
Literature review. H. W. T., D. L., M. L., K. Y. Y., W. H. L., K. L. C., and G. C.
Drafting of the manuscript. G. C. and M. K.
Figures. R. S.
Critical revision of the manuscript for important intellectual content. All authors.

Acknowledgments. The authors thank the Drug Office of the Department of Health and the Hospital Authority for providing vaccination and clinical data. They also thank Dr Bernard Chan, Wan-Mui Chan, Allen Wing-Ho Chu, and Jonathan Daniel Ip for their technical support and administrative assistance.

Financial support. Research grant from the Food and Health Bureau, the Government of the Hong Kong Special Administrative Region (ref. no. COVID19F01). I. C. K. W. reports support from Health and Medical Research Fund of Hong Kong Government (Ref: COVID19F01 to The University of Hong Kong).

Role of funding source. This is a regulatory pharmacovigilance study initiated by the Department of Health (DH) and funded by the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region. The corresponding author has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Potential conflict of interest. C. C. has received grants outside of the submitted work from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grants Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA, and Amgen; and a personal fee from Primevigilance Ltd. A. S. Y. L. received grants outside of the submitted work from the Health and Medical Research Fund, Food and Health Bureau of the Hong Kong Government Special Administrative Region. M. Y. N. has received funding/education grants from the Food and Health Bureau of the Hong Kong Government, Radiological Society of North America, GE, Lode, Arterys, Bayer, Circle Cardiovascular Imaging and Terarecon; honoraria for education activities from Boehringer Ingelheim; reports the following leadership roles: Vice Chair of the Education Committee for Society of Cardiovascular Magnetic Resonance and Member of the Corporate
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, HK SAR. 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, personal honoraria for Guerbet online lecture on pediatric cardiac imaging; holds 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.

References

1. Chua GT, Wong JSC, Lam I, et al. Clinical characteristics and transmission of COVID-19 in children and youths during 3 waves of outbreaks in Hong Kong. JAMA Network Open 2021; 4:e218824-e218824.
2. Tso WWY, Wong RS, Tung KTS, et al. Vulnerability and resilience in children during the COVID-19 pandemic. Eur Child Adolesc Psychiatry 2020; 7:1–16.
3. Persons aged 12 to 15 can make reservations to receive BNT162b2 vaccine from tomorrow. The Government of the Hong Kong Special Administrative Region. Available at: https://www.info.gov.hk/gia/general/202106/10/P2021061000556.htm. Accessed 22 July 2021.
4. Wan EYF, Chui CSL, Lai FTT, et al. Bell’s palsy following vaccination with mRNA Covid-19 Vaccine. N Engl J Med 2020; 383:2603–15.
5. Li X, Tong X, Yeung WWY, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis 2021; doi:10.1136/annrheumdis-2021-221571.
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383:2603–15. This study was supported by Pfizer Pharmaceutical. The authors have declared no other financial interests.
7. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring - United States, December 14, 2020–January 13, 2021. MMWR Morb Mortal Wkly Rep 2021; 70:283–8.
8. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics 2021; 148:e2021052478. doi:10.1542/peds.2021-052478.
9. Montgomery I, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military: JAMA Cardiology 2021; 6:1202–6.
10. 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; 70:977–82.
11. Young people aged 12 to 15 to be offered a COVID-19 vaccine. GOV.UK. Available at: https://www.gov.uk/government/news/young-people-aged-12-to-15-to-be-offered-a-covid-19-vaccine. Accessed 19 September 2021.
12. Myocarditis/Pericarditis Case Definition. Brighton Collaboration. Available at: https://brightoncollaboration.us/myocarditis-case-definition-update/1. Accessed 22 July 2021.
13. Table 1B: Population by Sex and Age. Census and Statistics Department, The Government of the HK SAR. Updated Aug 12, 2021. Available at: https://www.censatd.gov.hk/en/web_table.html?id=1B. Accessed 21 September 2021.
14. Kwan MYW, Chua GT, Chow CR, et al. mRNA COVID vaccine and myocarditis in adolescents. Hong Kong Med J 2021; 27:326–7.
15. Shay DK, Shimabukuro TT, DeStefano F. Myocarditis occurring after immunization with mRNA-based COVID-19 vaccines. JAMA Cardiology 2021; 6:1115–7. doi:10.1001/jamacardio.2021.2821.
16. Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine 2021; 39:3790–3.
17. Simone A, Herald J, Chen A, et al. Acute myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. JAMA Internal Medicine 2021; 181:1668–70. doi:10.1001/jama.2021.5511.
18. Li C, Chen Y, Zhao Y, et al. Intravenous injection of coronavirus disease 2019 (COVID-19) mRNA vaccine can induce acute myopericarditis in mouse model. Clin Infect Dis 2022; 74:1933–50.
19. Diaz GA, Parsons GT, Gerring SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA 2021; 326:1210–2. doi:10.1001/jama.2021.13443.
20. Starekova J, Bluemke DA, Bradham WS, et al. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging. JAMA Cardiol 2021; 6:945–50. doi:10.1001/jamacardio.2020.7444.
21. Ghafour K, Ahmed A, Abbas M. Fulminant myocarditis with ST elevation and cardiogenic shock in a SARS-CoV-2 patient. Cureus 2021; 7:e16149.
22. Malek I A, Marczak M, Milosz-Wiezorek B, et al. Cardiac involvement in consecutive elite athletes recovered from Covid-19: a magnetic resonance study. J Magn Reson Imaging 2021; 53:1723–9.
23. Chodick G, Tene L, Patalon T, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13–24 days after immunization: real-world evidence. medRxiv 2021; doi:10.1101/2021.01.27.21250612.
24. Latest situation of cases of COVID-19 (as of 18 November 2021) Centre for Health Protection, HK SAR. Available at: https://www.chp.gov.hk/files/pdf/local_situation_covid19_en.pdf. Accessed 19 November 2021.
25. Scientific Committees under CHP issue consensus interim recommendations on COVID-19 vaccination. The Government of the Hong Kong Special Administrative Region. Available at: https://www.info.gov.hk/gia/general/202109/15/P2021091501003.htm. Accessed 19 September 2021.