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COMPARISON OF FIRST AND SECOND WAVE COHORTS OF MULTISYSTEM INFLAMMATORY DISEASE SYNDROME IN CHILDREN
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Abstract: Comparing first and second wave MIS-C cohorts at our quaternary pediatric institution, second wave were older, presented more frequently with shortness of breath, higher maximum troponin and N-terminal BNP, and more frequently required advanced respiratory and intropic support. Despite increased severity in the second cohort, both cohorts had similar rates of coronary artery abnormalities, systolic dysfunction, and length of stay.

Key Words: pediatric multisystem inflammatory syndrome, PMIS, multisystem inflammatory syndrome in children, MIS-C, 2019 coronavirus disease, immunomodulation, myocarditis, critical care

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A.S.H. and M.P.S. was involved in study design, data gathering, data analysis, drafting, and editing of the article. E.A. was involved in data gathering, data analysis, and editing of the article. J.E.B. was involved in data analysis, drafting, and editing the article. D.W. was involved in study design, data analysis, and editing of the article. R.L.D. was involved in study design, data gathering, data analysis, drafting, and editing the article. All authors approved the final article as submitted and agree to be accountable for all aspects of the work. The members of Children’s National Hospital MIS-C Taskforce listed in Appendix.

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M ultisystem inflammatory syndrome in children (MIS-C) is a newly described severe hyperinflammatory multisystem illness specific to the pediatric population, which is thought to be an immune-mediated complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.1,2 Our center managed 2 distinct cohorts of MIS-C patients, each following periods of maximal virus circulation and surge (waves) in our community by 4–6 weeks. Multiple centers (including ours) and consortia, as well as the CDC, have published key demographic and clinical features of MIS-C following the first wave of patients with this rare presentation. These reports have included patients with varying degrees of severity, cardiac dysfunction, requirement for critical care, respiratory, inotropic, and immunomodulatory support.3–6 The second wave of MIS-C patients at our institution was larger than the first wave, following the largest surge in SARS-CoV-2 circulation in the United States and our community. Herein, we provide the first comparison of clinical features and outcomes for MIS-C patient cohorts treated at our facility during the first and second large waves of presentation, under a standard institutional evaluation and treatment protocol that prioritizes prompt immunomodulatory therapy.

MATERIALS AND METHODS
This was a prospective cohort study of 106 patients sequentially diagnosed and treated for MIS-C according to the Centers for Disease Control and Prevention MIS-C case definition and admitted to our quaternary pediatric center in Washington, DC.7 Patients’ demographic, clinical, laboratory, radiographic, including echocardiography, therapies, and outcomes were extracted from electronic medical records. Wave 1 MIS-C Cohort patients (N = 43) were hospitalized between March and October 2020; Wave 2 MIS-Cohort patients (N = 63) were hospitalized between November 2020 and April 2021. All patients were managed under the same standardized institutional protocol that utilizes intravenous immunoglobulin (IVIG) and aspirin with or without Anakinra as initial therapy, as well as escalation to additional corticosteroid immunomodulation depending on defined clinical parameters. The institutional algorithm was developed by a multidisciplinary committee (Children’s National Hospital MIS-C Task force).7,8 Cardiovascular complications were defined as abnormal coronary artery (Z score ≥ 2) or decreased systolic function (ejection fraction < 55% or shortening fraction < 28%).3–8

Statistical Analysis
The analysis compared the 2 MIS-C cohorts with respect to demographics, clinical features, diagnostic biomarkers, radiographic procedures including echocardiogram, immunomodulatory and vasopressor support, and clinical outcomes. All data were summarized using descriptive statistics of the median and interquartile (IQR) range and frequency. Continuous variables were analyzed using the nonparametric Wilcoxon rank sum test as normality was
not assumed. Categorical variables were analyzed using the χ² and Fisher’s exact test. A P ≤ 0.05 was considered statistically significant and P > 0.05 but <0.1 was considered a trend. All analyses were performed using STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Children’s National Hospital Institutional Review Board approved this study with a waiver of consent granted. Authors A.S.H., M.P.S., J.E.B., and R.L.D. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

The median patient age was 8.4 years (4.7–13.4), 49 (46%) were female, 56 (54%) were Black, and 41 (39%) were Hispanic. No underlying medical conditions were noted in 80 (75%) patients. Thirty-four (32%) met diagnostic criteria for Kawasaki disease (Table 1). No mortality occurred and all patients were discharged home at a median (IQR) of 11 (7–14) days.

Comparing MIS-C patient from the wave 1 and wave 2 cohorts, patients in Wave 2 included a higher proportion of children 15 years of age or older [13/63 (21%) vs. 2/43 (5%); P = 0.024]. Wave 2 cohort patients were less likely to fulfill diagnostic criteria for Kawasaki disease [13/63 (21%) vs. 21/43 (49%); P = 0.003] and more likely to present with shortness of breath [11/63 (18%) vs. 1/43 (3%); P = 0.025]. Wave 2 Cohort patients were less likely to be polymerase chain reaction-positive for SARS-CoV-2 [10/63 (16%) vs. 21/43 (49%); P < 0.001], had higher maximum median Troponin I (ng/mL) values [0.43 (IQR 0.14–1.665) vs. 0.145 (IQR 0.08–0.66); P = 0.022], and higher maximum N-terminal B-type natriuretic peptide (pg/mL) values [17,825.5 (IQR 7827–29,569) vs. 9780 (2426–17,886); P = 0.005]. Wave 2 cohort patients were more likely to require additional immunomodulation with methylprednisolone [18/63 (29%) vs. 3/43 (7%); P = 0.006] and a trend toward more frequent requirement for ICU level of care [51/63 (81%) vs. 28/43 (65%); P = 0.074]. Wave 2 cohort patients were more likely to require vasopressors [46/63 (73%) vs. 22/43 (51%); P = 0.025], had higher maximum vasactive index score [median 10 (IQR 0–20) vs. 3 (0–15); P = 0.042], had increased utilization of bi-level positive airway pressure (BiPAP) [25/63 (40%) vs. 8/43 (19%); P = 0.032], and were thus less likely to utilize only high flow nasal cannula [63/10% (26%) vs. 11/43 (32%); P = 0.033] (Table 1). Despite the increased degree of clinical severity and laboratory abnormalities in the wave 2 cohort, no significant differences were noted comparing wave 2 and wave 1 cohorts with respect to rate of coronary artery abnormalities [3/56 (5%) vs. 6/41 (15%); P = 0.16], systolic dysfunction [17/58 (29%) vs. 12/37 (32%); P = 0.821] or length of stay [10 days (IQR 8–14) vs. 12 days (IQR 7–14); P = 0.437] (Table 1).

DISCUSSION

Our center managed a large number of MIS-C patients under a standardized MIS-C evaluation and treatment algorithm throughout the first year of SARS-CoV-2 circulation in the United States, with 2 distinct cohorts of MIS-C patients presenting 4–6 weeks following 2 distinct large waves of viral circulation and primary COVID infection and admissions in our region. In the second (later) wave following the largest surge of virus in the United States, MIS-C patients presented with more severe respiratory and cardiovascular symptoms, had more abnormal BNP and Troponin levels, had a tendency for more frequently requiring ICU level of support, more frequently required inotropic and advanced respiratory support. Although a larger proportion of patients in the Wave 2 Cohort met criteria for escalation of immunomodulation to include adjunctive corticosteroid therapy (in addition to first line IVIG and aspirin with or without anakinra), the majority of wave 1 and wave 2 patients did not require escalation to methylprednisolone (93% wave 1 cohort; 71% wave 2 cohort). Despite the overall increased severity of disease observed in the wave 2 cohort, the incidence of coronary artery abnormalities and ventricular systolic dysfunction were not different between the 2 cohorts.

The reasons for the observed increased clinical severity at presentation in the wave 2 cohort are not entirely clear, but were not due to differences in underlying sex, race, or ethnicity (overwhelmingly Black or Hispanic), or presence of underlying medical condition which were similar in both cohorts. The exact immunologic mechanisms by which MIS-C is triggered and the specific factors accounting for its rare occurrence are still not fully understood. However, in comparison to the wave 1 cohort, children in the wave 2 MIS-C cohort had potentially experienced additional intermittent or multiple repeated exposure(s) to circulating SARS-CoV-2 virus in their communities, which may have served as repeated immune triggers to augment or accelerate the dysregulated hyperimmune response that is unique to MIS-C. Differences in the proportion of circulating variants within the time periods defining each cohort could also have contributed to differences in degree of immune dysregulation; it should be noted that there was minimal circulation of the delta variant in the United States or our community during either period. The timing and characterization of a potential third delta variant-associated MIS-C surge remains to be seen, but has not yet materialized at our institution, despite 7 weeks since inception of our current SARS-CoV-2 surge.

Strengths of this study include the ability to compare well characterized cohorts accurately, since a single, standardized evaluation, and treatment approach was used at a single site across the entire period for the study, encompassing both waves of MIS-C presentation. Protocollization and standardization of care has been shown to improve patient care.9 Despite more severe clinical presentation and a higher degree of laboratory abnormalities, children in the second wave MIS-C cohort had a similar, not increased, incidence of cardiac abnormalities, length of stay, and outcome with no mortality in either cohort. Belay et al reported an increased need for immunotherapy in MIS-C patients presenting later in the pandemic, that was also associated with a lower incidence of cardiac dysfunction.10 The standardized approach implemented at our center was associated with stable rates of cardiac complications despite more severe clinical presentation in the more recent MIS-C cohort (wave 2). Limitations of our study include the fact that we limited cardiac complications for comparison to coronary artery abnormalities or decreased systolic function, and did not include valvular regurgitation or pericardial effusion, although in our overall institutional cohort, these findings have been observed to be the most transient and likely to resolve during short-term follow-up.11

CONCLUSIONS

MIS-C remains a diagnostic and therapeutic challenge for pediatricians and subspecialists. Although a spectrum of clinical severity has been observed across centers, this report highlights that severity of disease may also evolve over different time points of the pandemic. Despite increased severity, mortality was prevented, and morbidity was mitigated with rapid implementation of a standardized, protocollized, and coordinated immunomodulatory approach.

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# MIS-C First and Second Wave Cohort Comparison

## TABLE 1. Demographics, Patient Characteristics, Laboratory findings, Diagnostics, Treatments, Clinical Outcomes and Echocardiographic Findings Among MIS-C Patients Stratified by Wave Cohort

| Variable of Interest                                      | All Cases (N = 106) n (%) | Wave 1 Cohort (N = 43) n (%) | Wave 2 Cohort (N = 63) n (%) | P value Wave 1 vs. Wave 2 Cohort |
|-----------------------------------------------------------|---------------------------|-----------------------------|-----------------------------|---------------------------------|
| **Demographics**                                          |                           |                             |                             |                                 |
| Age in months (median and IQR)                           | 101 (56–161)              | 95 (44–151)                 | 109 (61–171)                | 0.126                           |
| Specific age bands all patients                          |                           |                             |                             |                                 |
| <1                                                        | 2 (2%)                    | 1 (2%)                      | 1 (2%)                      | 0.173                           |
| 1–<5                                                      | 27 (25%)                  | 13 (30%)                    | 14 (22%)                    |                                 |
| 5–<10                                                     | 35 (33%)                  | 15 (35%)                    | 20 (32%)                    |                                 |
| 10–<15                                                    | 27 (25%)                  | 12 (28%)                    | 15 (24%)                    |                                 |
| 15+                                                       | 15 (14%)                  | 2 (5%)                      | 13 (21%)                    |                                 |
| Specific age bands all patients                          |                           |                             |                             | 0.024                           |
| <15                                                       | 91 (88%)                  | 41 (95%)                    | 50 (79%)                    |                                 |
| ≥15                                                       | 15 (14%)                  | 2 (5%)                      | 13 (21%)                    |                                 |
| Sex (% Female)                                           |                           |                             |                             |                                 |
| Presence of any underlying condition                     | 26 (25%)                  | 13 (30%)                    | 13 (21%)                    | 0.358                           |
| Known sick contact                                       | 33 (34%)                  | 15 (39%)                    | 18 (31%)                    | 0.513                           |
| N = 98                                                    | N = 39                    | N = 59                      |                             |                                 |
| Presence of Kawasaki disease Criteria                    | 34 (32%)                  | 21 (49%)                    | 13 (21%)                    | 0.003                           |
| Specific Symptoms                                         |                           |                             |                             |                                 |
| Mucous membrane changes                                  | 62 (58%)                  | 29 (67%)                    | 33 (52%)                    | 0.160                           |
| Peripheral extremity changes                             | 14 (13%)                  | 7 (17%)                     | 7 (11%)                     | 0.559                           |
| Conjunctival injection                                   | 56 (53%)                  | 26 (60%)                    | 30 (48%)                    | 0.236                           |
| Rash                                                      | 49 (46%)                  | 19 (44%)                    | 30 (48%)                    | 0.843                           |
| Fever                                                     | 104 (98%)                 | 42 (98%)                    | 62 (98%)                    | 0.999                           |
| Cough                                                     | 18 (17%)                  | 9 (21%)                     | 9 (14%)                     | 0.432                           |
| Shortness of breath                                      | 12 (12%)                  | 1 (3%)                      | 11 (18%)                    | 0.025                           |
| Abdominal pain                                            | 79 (75%)                  | 35 (81%)                    | 44 (70%)                    | 0.256                           |
| Vomiting                                                  | 65 (61%)                  | 25 (59%)                    | 38 (62%)                    | 0.838                           |
| Diarrhea                                                  | 50 (49%)                  | 19 (46%)                    | 31 (51%)                    | 0.690                           |
| Chest pain                                                | 12 (14%)                  | 2 (7%)                      | 10 (17%)                    | 0.321                           |
| Myalgias                                                  | 24 (23%)                  | 9 (30%)                     | 15 (26%)                    | 0.801                           |
| Laboratory findings                                       |                           |                             |                             |                                 |
| SARS-CoV-2 PCR positive                                  | 31 (29%)                  | 21 (49%)                    | 10 (16%)                    | <0.001                          |
| N = 106                                                   | N = 43                    | N = 63                      |                             |                                 |
| SARS-CoV-2 PCR cycle time (median and IQR)               | 32 (30–33.1)              | 31.3 (28–32.65)             | 32.6 (32.2–33.7)            | 0.069                           |
| N = 28                                                    | N = 19                    | N = 9                       |                             |                                 |
| SARS-CoV-2 Antibody positive (median and IQR)            | 0.35 (0.09–1.04)          | 0.145 (0.08–0.66)           | 0.43 (0.14–1.665)           | 0.022                           |
| N = 98                                                    | N = 38                    | N = 60                      |                             |                                 |
| Troponin I–maximum (ng/mL) (Normal <0.04)             | 12.991 (4617.5–23,478.5)  | 9780 (2426.5–17,886)        | 17,825.5 (7827–29,569)      | 0.005                           |
| N-terminal B-type natriuretic peptide–maximum (pg/mL)    |                           |                             |                             |                                 |
| N = 104                                                  | N = 42                    | N = 62                      |                             |                                 |
| Diagnostics                                              |                           |                             |                             |                                 |
| Chest radiograph abnormal                                | 60 (61%)                  | 27 (64%)                    | 33 (59%)                    | 0.677                           |

(Continued)
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| Variable of Interest | All Cases (N = 106) | Wave 1 Cohort (N = 43) | Wave 2 Cohort (N = 63) | P value Wave 1 vs. Wave 2 Cohort |
|----------------------|--------------------|----------------------|----------------------|---------------------------------|
| **Treatments**       |                    |                      |                      |                                 |
| Intravenous immunglobulin (IVIG) | 105 (99%) | 42 (98%) | 63 (100%) | 0.406                          |
| Anakinra             | 78 (74%)          | 31 (72%)            | 47 (75%)            | 0.824                          |
| Steroids             | 37 (37%)          | 10 (24%)            | 27 (44%)            | 0.090                          |
| Hydrocortisone       | 22 (21%)          | 7 (17%)             | 15 (24%)            | 0.466                          |
| Dexamethasone        | 3 (3%)            | 2 (5%)              | 1 (2%)              | 0.565                          |
| Methylprednisolone   | 21 (20%)          | 3 (7%)              | 18 (29%)            | 0.006                          |
| Tocilizumab          | 3 (3%)            | 0 (0%)              | 3 (5%)              | 0.261                          |
| Remdesivir           | 1 (1%)            | 0 (0%)              | 1 (2%)              | 0.999                          |
| Aspirin              | 102 (96%)         | 41 (95%)            | 61 (97%)            | 0.999                          |
| ICU admission        | 79 (75%)          | 28 (65%)            | 51 (81%)            | 0.074                          |
| Vasopressors         | 68 (64%)          | 22 (51%)            | 46 (73%)            | 0.025                          |
| Vasovactive Index (VIS) Score (Maximum) (median and IQR) | 5 (3) | 10 | 0.042 |
| Coronary artery abnormalities | 97 | 41 | 56 | 0.161 |
| No (Z score < 2)     | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Yes (Z score ≥ 2)    | 9 (9%)            | 6 (15%)             | 3 (5%)              |                                 |
| Coronary Artery classifications | 97 | 41 | 56 | 0.174 |
| Normal (Z score < 2) | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Dilation (Z score 2 to < 2.5) | 7 (7%) | 4 (10%) | 3 (5%) |                                 |
| Small aneurysm (Z score 2.5 to <5) | 2 (2%) | 2 (5%) | 0 (0%) |                                 |
| Moderate aneurysm (Z score 5 to <10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Giant aneurysm (8 mm or Z score ≥ 10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Ejection fraction (EF) continuous variable (%) | 60 | 60 | 60 | 0.625 |
| Coronary Artery classifications | 97 | 37 | 58 | 0.821 |
| No (Z score < 2)     | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Yes (Z score ≥ 2)    | 9 (9%)            | 6 (15%)             | 3 (5%)              |                                 |
| Coronary Artery classifications | 97 | 37 | 58 | 0.868 |
| Normal (Z score < 2) | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Dilation (Z score 2 to < 2.5) | 7 (7%) | 4 (10%) | 3 (5%) |                                 |
| Small aneurysm (Z score 2.5 to<5) | 2 (2%) | 2 (5%) | 0 (0%) |                                 |
| Moderate aneurysm (Z score 5 to <10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Giant aneurysm (8 mm or Z score ≥ 10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Ejection fraction (EF) continuous variable (%) | 60 | 60 | 60 | 0.625 |
| Coronary Artery classifications | 97 | 37 | 58 | 0.868 |
| Normal (Z score < 2) | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Dilation (Z score 2 to < 2.5) | 7 (7%) | 4 (10%) | 3 (5%) |                                 |
| Small aneurysm (Z score 2.5 to <5) | 2 (2%) | 2 (5%) | 0 (0%) |                                 |
| Moderate aneurysm (Z score 5 to <10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Giant aneurysm (8 mm or Z score ≥ 10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Ejection fraction (EF) continuous variable (%) | 60 | 60 | 60 | 0.625 |
| Coronary Artery classifications | 97 | 37 | 58 | 0.868 |
| Normal (Z score < 2) | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Dilation (Z score 2 to < 2.5) | 7 (7%) | 4 (10%) | 3 (5%) |                                 |
| Small aneurysm (Z score 2.5 to <5) | 2 (2%) | 2 (5%) | 0 (0%) |                                 |
| Moderate aneurysm (Z score 5 to <10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Giant aneurysm (8 mm or Z score ≥ 10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Ejection fraction (EF) continuous variable (%) | 60 | 60 | 60 | 0.625 |
| Coronary Artery classifications | 97 | 37 | 58 | 0.868 |
| Normal (Z score < 2) | 88 (91%)          | 35 (85%)            | 53 (95%)            |                                 |
| Dilation (Z score 2 to < 2.5) | 7 (7%) | 4 (10%) | 3 (5%) |                                 |
| Small aneurysm (Z score 2.5 to <5) | 2 (2%) | 2 (5%) | 0 (0%) |                                 |
| Moderate aneurysm (Z score 5 to <10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Giant aneurysm (8 mm or Z score ≥ 10) | 0 (0%) | 0 (0%) | 0 (0%) |                                 |
| Ejection fraction (EF) continuous variable (%) | 60 | 60 | 60 | 0.625 |

BiPAP, bi-level positive airway pressure; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

TABLE 1. (Continued)
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APPENDIX

ADDITIONAL MIS-C-TASK FORCE CONTRIBUTORS

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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.12

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

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

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