The Impact of SARS-CoV-2 Variants on the Clinical Phenotype and Severity of Multisystem Inflammatory Syndrome in Children in South Africa

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Abstract: The effects of SARS-CoV-2 variants on disease phenotype and severity of multisystem inflammatory syndrome in children (MIS-C) are unknown. We compared the clinical phenotype of MIS-C in 129 South African children across four distinct (Ancestral, Beta, Delta, and Omicron) variant-driven waves and found that MIS-C remains a severe disease with a stable clinical presentation, regardless of variant.

Key words: multisystem inflammatory syndrome in children, MIS-C, variants of concern, VOC, coronavirus disease 2019, COVID-19

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Multisystem inflammatory syndrome in children (MIS-C) is a severe postinfectious hyperinflammatory complication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in children and adolescents. The exact viral and immune factors driving MIS-C remain unclear.

There are no data linking the incidence of MIS-C and disease severity to the different variants of concern (VOC) from Africa. It is unknown whether increasing community SARS-CoV-2 seroprevalence will decrease the pool of infection-naïve children and mitigate the incidence and clinical phenotype of MIS-C with new VOC in areas with restricted childhood SARS-CoV-2 vaccinations.

To date, South Africa has recorded 4 distinct SARS-CoV-2 waves: Ancestral, Beta, Delta and Omicron. The first case of MIS-C in Cape Town was reported on 7 May 2020 and since then cases have been comprehensively documented at 2 tertiary hospitals in Cape Town, South Africa: Tygerberg Hospital (TBH) and Red Cross War Memorial Children Hospital (RCCH).

This is a retrospective study of MIS-C cases from 4 variant-driven waves to determine whether there were notable differences in the number of cases, presentation, severity and early clinical outcomes.

MATERIALS AND METHODS

Children diagnosed with MIS-C as per the World Health Organization (WHO) criteria at TBH and RCCH from May 1, 2020, to March 31, 2022, were included. Demographic, epidemiologic and clinical data have been described previously for 68 of the participants. The National Institute of Communicable disease (NICD) Genomic Surveillance reports were used to define the timing of waves and the VOC associated with each wave: Ancestral from May 3, 2020, to August 16, 2020, Beta from November 8, 2020, to February 7, 2021; Delta from May 23, 2021, to September 19, 2021; and Omicron from November 28, 2021, to January 30, 2022.

All cases were reviewed to ensure they met the WHO case definition for MIS-C. De-identified demographic, clinical, laboratory, imaging and outcome data were recorded as described previously. Children with MIS-C were allocated to a VOC wave if they presented with MIS-C between the start of a wave and the beginning of the next wave.

Data were analyzed using IBM SPSS Statistics, Version 28.0. Medians and interquartile ranges were reported for non-parametric data. Comparison of proportions was measured using Chi-squared or Fisher exact test, where appropriate and continuous data were summarized using an independent sample t-test or Mann-Whitney U tests.

The Ethics approvals were provided by Stellenbosch University (N20/07/041 and N20/04/013), University of Cape Town (112/2012, 599/2020 and RCC240/WC_202008_113) research ethics committees.
RESULTS

One hundred twenty-nine children, 63 (48.8%) from TBH and 66 (51.2%) from RCCH, were recorded between May 1, 2020, and March 31, 2022 (Figure 1). None of the children were vaccinated against COVID-19. One child from the Omicron wave was eligible for vaccination at the time of developing MIS-C as per national vaccination guidelines.5

Forty-nine (38.0%) cases were reported in wave 1 (Ances-
tral), 21 (16.3%) in wave 2 (Beta), 43 (33.3%) in wave 3 (Delta), and 16 (12.4%) in wave 4 (Omicron) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811). There was a lower proportion of black versus mixed race children in the third wave compared to other waves (32.6% vs. 51.2% overall, P = 0.02). The median patient age was 6.85 years (interquartile range [IQR], 3.39–9.28), with a trend of a decreasing median age with each consecutive wave with the lowest median age recorded in the fourth wave: wave 1: 7.37 (IQR, 3.39–10.00); wave 2: 7.30 (IQR, 4.17–7.84); wave 3: 6.37 (IQR, 4.20–9.11); wave 4: 4.93 (IQR, 2.63–8.27) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811). There was a lower proportion of black versus mixed race children in the third wave compared to other waves (32.6% vs. 51.2% overall, P = 0.02). The median patient age was 6.85 years (interquartile range [IQR], 3.39–9.28), with a trend of a decreasing median age with each consecutive wave with the lowest median age recorded in the fourth wave: wave 1: 7.37 (IQR, 3.39–10.00); wave 2: 7.30 (IQR, 4.17–7.84); wave 3: 6.37 (IQR, 4.20–9.11); wave 4: 4.93 (IQR, 2.63–8.27) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811). There was a lower proportion of black versus mixed race children in the third wave compared to other waves (32.6% vs. 51.2% overall, P = 0.02). The median patient age was 6.85 years (interquartile range [IQR], 3.39–9.28), with a trend of a decreasing median age with each consecutive wave with the lowest median age recorded in the fourth wave: wave 1: 7.37 (IQR, 3.39–10.00); wave 2: 7.30 (IQR, 4.17–7.84); wave 3: 6.37 (IQR, 4.20–9.11); wave 4: 4.93 (IQR, 2.63–8.27) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811).

There was no difference between waves in the proportion of children with skin rash (P = 0.79), conjunctivitis (P = 0.21), or abdominal pain (P = 0.63), but there was a lower rate of diarrhea in the fourth wave (28/49 vs. 13/21 vs. 19/43 vs. 3/16; P = 0.03). There was no difference between waves in the proportion of children with specific organ involvement. Central nervous system (CNS) involvement was present in nearly one-third of all patients with the highest proportion in the third wave (16/43; 37.2%) and lowest in the fourth wave (2/16; 12.5%, P = 0.31). Thirty-eight patients (29.5% of overall cohort) had renal involvement; 14/49 (28.6%) in the first wave, 5/12 (41.6%) in the second wave, 17/43 (39.5%) in the third wave, and 2/16 (12.5%, P = 0.21) in the fourth wave (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811).

Seventeen of 128 (13.3%) children had a positive SARS-
CoV-2 Polymerase Chain Reaction (PCR) test result with no difference between waves (P = 0.67). Overall, 43/129 (33%) of children required inotropic blood pressure support and 49/129 (38%) required intensive care unit (ICU) admission with no difference in the requirement for inotropes (P = 0.60) or ICU admission (P = 0.90) per wave. The median time from symptom onset to admission was 4 days (interquartile range [IQR], 3–6) with no difference between waves (P = 0.54). The median duration of hospital admission was 7 days (IQR, 6–10) with no difference between waves (P = 0.67) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811).

The estimated median CRP was 213 mg/L (IQR, 127–302), ferritin 552 ng/L (IQR, 287–1020), and pro-BNP 3696 ng/L (IQR, 718–15,259). Sodium, d-dimer and fibrinogen were markedly abnormal with IQR estimates outside of the normal range. There was however no difference in the estimated median value of any of these blood test results in between waves (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811).

Abnormal echocardiogram (ECHO) findings were common, with 70.9% of all cases showing an abnormal result. The proportions remaining relatively constant across the 4 waves; with abnormal ECHO findings seen in 75.7%, 66.7%, 66.7% and 73.3% over the different waves (P = 0.72), respectively. Coronary artery abnormalities were seen more commonly in the second and third waves compared with the first and fourth waves (P = 0.06). Ejection fraction (EF) was decreased in most patients, with a median of 59% (IQR, 47–65), with lowest value in the first wave compared with the other waves (51%, 64%, 61% and 58%, P = 0.07) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E811).

DISCUSSION

Here, we report that, in our setting, the clinical presentation, laboratory features and disease course of MIS-C did not change markedly with each new variant-driven wave and that MIS-C remained a distinct and severe childhood disease. Despite increased awareness of MIS-C, the duration of symptoms before diagnosis did not change.

Data from the United Kingdom suggest that compared with the Alpha wave, MIS-C was less common in the waves driven by Delta and Omicron,4 while a Danish study has shown that the risk of MIS-C was lower in the Omicron wave.7 We also report that fewer children required admission with MIS-C during the Omicron wave in Cape Town despite it being considered the most transmissible VOC driving a significant surge in COVID-19 pediatric hospitalizations.8 In contrast, the number of MIS-C admissions for Ances-
tral and Delta waves were similar. The lack of reliable denominator data for variant-specific pediatric SARS-CoV-2 infections makes it challenging to estimate the variant-related incidence of MIS-C. It has been proposed that ongoing immunity via vaccina-
tion; boosting or infection may result in MIS-C becoming similar to Kawasaki Disease (KD), in terms of becoming a sporadic condition.
affecting immunologically naïve infants and toddlers. We cannot determine from our data whether children with MIS-C developed it after their first or subsequent infection with SARS-CoV-2. The decreasing numbers of cases with time, in a largely unvaccinated population with lack of reports of children developing MIS-C twice, does imply that the risk may be associated with immunologic naivety to SARS-CoV-2. In this study, the lowest median age of children with MIS-C was reported in the Omicron wave, along with lower rates of diarrhea, which may reflect the trend towards MIS-C resembling the clinical phenotype of KD over time. If this continues, differentiation between KD and MIS-C may become challenging. The clinical case definition of MIS-C as per the WHO will need revision as increasing seroprevalence and evidence of prior infection with SARS-CoV-2 will not allow for differentiation.

South Africa approved use of 2 doses of Pfizer-BioNTech COVID-19 vaccines for those 12–17 years of age in late October 2021, with poor uptake, and few younger people receiving vaccination before the Omicron wave. We could not determine whether vaccination affected the risk of developing MIS-C in this population as reported elsewhere. Our observations are from a largely unvaccinated population and may not extrapolate to highly vaccinated populations.

Cases were classified into variants from the start of 1 wave up until the start of the next which may introduce a small margin of error. Other limitations of the study include the small sample size within waves, heterogeneous investigations and management, and bias, given that these are all hospitalized children. The setting of this study within a low middle-income country provides important data that may be extrapolated to similar settings.

MIS-C remains a challenging and life-threatening postinfectious complication of SARS-CoV-2 infection affecting children and adolescents. MIS-C persisted despite 4 distinct variant-driven waves, with the least cases in the fourth Omicron wave. Early outcomes were generally good, with only 1 MIS-C related death. Whether newer COVID-19 variants, natural immunity and COVID-19 vaccination will have an impact on the risk of MIS-C, lower the incidence or even prevent its presentation in subsequent waves, remains to be determined.

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