Lower Risk of Multisystem Inflammatory Syndrome in Children (MIS-C) with the Delta and Omicron variants of SARS-CoV-2

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Abstract

Little is known about the MIS-C risk with different SARS-CoV-2 variants. In Southeast England, MIS-C rates per confirmed SARS-CoV-2 infections in 0-16 years-olds were 56% lower (rate ratio, 0.34; 95%CI, 0.23-0.50) during pre-vaccine Delta, 66% lower (0.44; 0.28-0.69) during post-vaccine Delta and 95% lower (0.05; 0.02-0.10) during the Omicron period.

Key words: SARS-CoV-2, coronavirus, COVID-19, PIMS-TS, MIS-C

Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C, also known as PIMS-TS) is an acute inflammatory disorder, sharing features of Kawasaki disease and toxic-shock syndrome, typically occurring 2-6 weeks after SARS-CoV-2 exposure, mainly in children and young people (CYP). First described in England in April 2020,[1] this condition is now reported worldwide. Early estimates suggested a risk of MIS-C of 1 in 3-4,000 infected children.[2,3] Whether this risk is sustained with new SARS-CoV-2 variants remains unknown. We compared daily cases of MIS-C against SARS-CoV-2 infection in children in a defined geographical area of Southeast England to determine relative rates of MIS-C during Alpha, Delta and Omicron waves over a 22-month period.

Methods

Data Sources

We utilised prospective hospital admission data from the NHS South Thames Paediatric Network (STPN), which manages all MIS-C cases amongst 1·5 million children in South-East England, to assess trends over time. All patients 0–16 years with suspected MIS-C in the Network are discussed in a daily multi-disciplinary meeting, with diagnosis made according to RCPCH criteria, unchanged since September 2020.[4]

We compared MIS-C cases with two independent SARS-CoV-2 infection datasets. We used publicly available UK Health Security Agency (UKHSA) case numbers aggregated for age bands 0–4, 5–9 and 9–14 years across London and South East England, which records daily positive PCR and rapid-antigen tests from both healthcare and community testing within defined geographical regions.[5] These were matched to STPN catchment, weighting cases to reflect child population distributions according to area population estimates from Office for National Statistics (ONS).[6] Since this dataset could potentially be biased by evolving changes in testing behaviour, we also compared MIS-C cases to community infection rates in 2-11 year olds, obtained from ONS COVID-19 Infection Survey.[7] This

survey randomly selects individuals in private households for fortnightly PCR tests, deriving estimates of proportions infected in different age-groups irrespective of symptom status.

Normalisation and Data Presentation

All three datasets were independently normalised to the peak of the Alpha variant wave in January 2021, allowing comparison with future waves, and plotted against time. MIS-C cases were smoothed over 7 days and plotted against a date corresponding to 40 days prior to their hospital admission, allowing for the lag from SARS-CoV-2 infection to hospitalisation. This interval provided the closest parallel in rise of SARS-CoV-2 infection and MIS-C cases during the Alpha variant wave.

Definition of Variant Wave time periods

Using publicly available data on relative incidence of SARS-CoV-2 variants, we defined conservative time periods for each variant wave as the dates the specific variant was responsible for ≥90% of typed cases in both the London and SE England regions.[8,9,10] These correspond to 28 December 2020 to 7 March 2021 (Alpha), 13 June 2021 to 5 December 2021 (Delta) and 25 December 2021 to 1 Feb 2022 (Omicron). To control for the possible contribution of vaccination to changing MIS-C rates, an even more conservative period of Delta variant wave was defined by restricting the time period until 12 September 2021 (week 36, 2021), when COVID-19 vaccination was first recommended for 12-15-year-olds in England.

Calculation of relative incidence of MIS-C

We calculated MIS-C incidence rates in two ways, using both the reported SARS-CoV-2 infection rates and community SARS-CoV-2 positivity rates as independent denominators. MIS-C cases were used as raw case numbers in the defined time periods as above. SARS-CoV-2 infection rates published by UKHSA and smoothed over 30 days were used as denominators to calculate MIS-C rates for each of the time periods above.

In the second analysis, the ONS COVID infection Survey provided estimates of percentage positivity at fortnightly time points. These values were imputed on an unchanged basis to the prior 13 days, and then summed over each of the defined time-periods to estimate infection rates, which were then used to calculate MIS-C rates. Using Alpha period as baseline, we calculated relative rate ratios with 95% confidence intervals (CI) in MIS-C rates during pre-vaccine Delta, post-vaccine Delta and Omicron periods.

Results

Compared with Alpha wave, we found fewer MIS-C cases relative to SARS-CoV-2 infections during both pre-vaccine Delta, post-vaccine Delta and Omicron waves in CYP (Figure 1). Using confirmed SARS-CoV-2 infection cases as the denominator, MIS-C cases were 56% lower (rate ratio, 0.34; 95%CI, 0.23-0.50; P<0.001) during pre-vaccine Delta period compared to Alpha period, 66% lower (0.44; 95%CI, 0.28-0.69; P<0.001) during post-vaccine Delta and 95% lower (0.05; 95%CI, 0.02-0.10; P<0.001) during Omicron period compared to Alpha variant wave (1 in 432 cases during Alpha, 1 in 977 during pre-vaccine Delta, 1 in 1260 during post-vaccine Delta and 1 in 8315 during Omicron). Using community infection positivity rates in 2–11-year-olds from ONS COVID Infection Survey as the denominator, the relative rates were 59%, 62% and 94% lower, respectively.

Discussion

Testing for SARS-CoV-2 infection was not widely available during the first pandemic wave caused by the wild-type Wuhan strain in Spring 2020. Consequently, we did not include the first wave in this analysis and, instead, used the Alpha wave as a benchmark. Free, accessible community PCR testing became widely available in England since June 2020 and, from March 2021, secondary school-aged students (11–18 year-olds) were asked to undertake twice-weekly home testing using rapid-antigen tests and report their results online. Despite the increased testing practices, patterns of reported

infections closely matched those of the ONS COVID-19 Infection Survey, which captured both symptomatic and asymptomatic infections in each age-group in the community every two weeks throughout the surveillance period. Reassuringly, MIS-C rates in children were very similar with both denominators, indicating true change in relative incidence of MIS-C during the different SARS-CoV-2 variant waves. The UK RCPCH definition of MIS-C (PIMS-TS)[4] differs from CDC and WHO definitions in not requiring evidence of recent SARS-CoV-2 infection. This may overestimate cases compared to these definitions. This did not change during the duration of this study so relative differences over time remain internally valid. There were proportionately fewer paediatric intensive care unit admissions in Delta compared to Alpha, likely reflecting earlier recognition and treatment. This could have led to over-diagnosis amongst less severely ill children, and would give rise to even greater differences between waves than we report here.

The lower MIS-C incidence during the pre-vaccine Delta wave was unlikely to be due to immunity from prior SARS-CoV-2 infection because nearly all Delta variant infections in children were primary infections and re-infections with Delta variant in children were uncommon during that period.[11] Recent studies have shown that mRNA vaccination against COVID-19 helps protect against MIS-C. For this reason, we assessed MIS-C risk during the Delta wave before and after COVID-19 vaccination was recommended for 12-15 year-olds in England. The lower MIS-C rate in the pre-vaccine Delta period in comparison to the Alpha wave is, therefore, unlikely to be due to vaccination. Additionally, compared to many other countries, COVID-19 vaccine uptake among adolescents in England has been low, with only half of 12-15 years receiving the first dose by the end of 2021,[12] while vaccination for 5–11-year-olds is planned for spring 2022. This likely explains the similar MIS-C rate reductions in the pre-vaccine and post-vaccine Delta periods compared to the Alpha wave. While prior infection and vaccination are unlikely to explain the lower MIS-C rates in the Delta wave, a more likely explanation may be viral mutations in key antigenic epitopes responsible for triggering the hyper-inflammatory response observed with MIS-C.

The more recent Omicron wave, which first emerged in November 2021, was associated with very high cases numbers but we found an even lower relative MIS-C risk compared with previous variants. When the Omicron variant emerged in England more than half the primary school-aged children (up to 11 years) and nearly all secondary-school aged children (12-15) had SARS-CoV-2 antibodies consistent with prior infection and/or vaccination.[13] Omicron possesses a number of new mutations in addition to those present in the Alpha, Beta and Delta variants, which allows the variant to at least partially evade both natural and vaccine-induced immunity, resulting in high rates of re-infections in previously-infected and vaccinated populations.[14] Mutations such as N679K may diminish superantigenicity reducing risk of MIS-C.[15] Consequently, the relative contributions of host immunity and viral changes to the even lower MIS-C rates during the Omicron wave are obscured.

Both of the denominator data sets used have limitations. Changing testing behaviour as a bias of community infection rates is controlled for by using the ONS COVID Infection Survey data, which estimates infection rates by age group irrespective of symptom status and provides regionally- and nationally-representative community infection rates at fortnightly intervals. The finding of very similar rate reductions with the different variants using two independent denominators provides confidence that these findings are real and reflect true ongoing changes in incidence in the community which is consistent with our clinical experience on the frontline.

As more children become immune through natural SARS-CoV-2 infection and/or vaccination, and with the on-gong boosting of immunity following reinfections with the omicron variant, we predict that MIS-C will behave as a sporadic condition occurring mainly in immunologically naive and genetically susceptible infants and toddlers.

NOTES

Author Contributions

JMC and MJC conceived the idea. Methodology was designed and formal analysis performed by JMC, and verified by MJC. Data interpretation was performed by JMC, MJC, SL and CRC. The manuscript was written by JMC, MJC, SL and CRC.

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Conflict of Interest

None of the authors have a conflict of interest to declare.

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Figure Legends

Figure 1

Relative cases of Multisystem Inflammatory Syndrome in Children (MIS-C) compared to rates of SARS-CoV-2 infection cases (UK Health Security Agency, UKHSA) and SARS-CoV-2 positivity estimates (Office for National Statistics, (ONS) in children in the South Thames Paediatric Network (STPN).

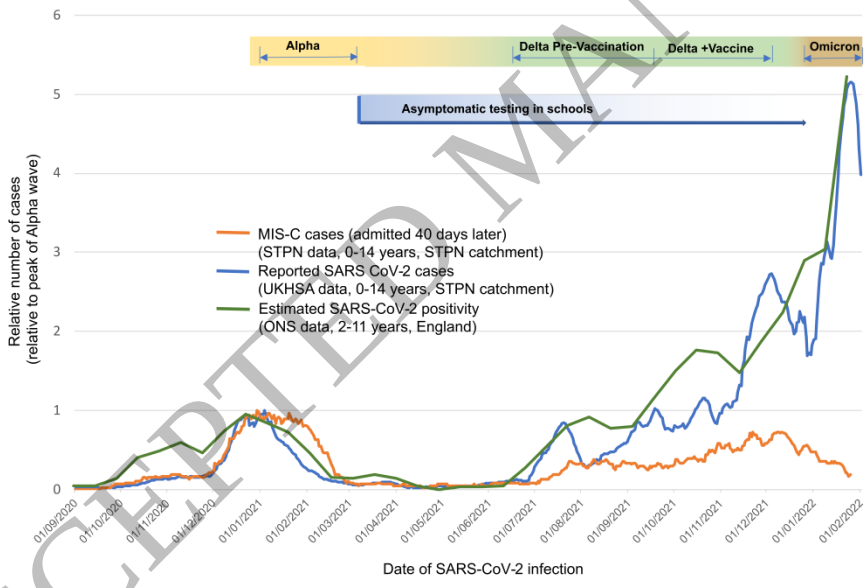

Figure 1
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