Lower Risk of Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) with the Delta variant of SARS-CoV-2

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Paediatric Inflammatory Multisystem Syndrome (PIMS-TS, also known as MIS-C) typically occurs 2-6 weeks after exposure to SARS-CoV-2. Early estimates suggested a risk of PIMS-TS of 1 in 3-4000 infected children. Whether this risk is sustained with new SARS-CoV-2 variants remains unknown.

We utilised prospective data from the NHS South Thames Paediatric Network (STPN), which manages all cases of PIMS-TS amongst 1.5 million children in South-East England, to assess trends over time. We compared PIMS-TS cases with two independent SARS-CoV-2 infection datasets. We used publicly available UK Health Security Agency case numbers weighted to child population distributions according to area population estimates from the Office for National Statistics (ONS). To avoid bias due to evolving testing behaviour, we also compared PIMS-TS cases to community infection rates, obtained from the ONS COVID-19 Infection Survey, which randomly selects individuals for fortnightly PCR tests. All three datasets were normalised to the peak of the Alpha wave, and plotted against time. PIMS-TS cases were plotted 40 days prior to hospitalisation, corresponding to the best fit of rising SARS-CoV-2 infection and PIMS-TS cases during the Alpha wave.

Compared with the Alpha wave, we found fewer cases of PIMS-TS relative to SARS-CoV-2 infections during both initial and subsequent Delta waves. This relative reduction continued into the Omicron wave.

Re-infection rates with the Alpha or Delta variants and vaccination rates were very low during the Delta wave. As a result, lower PIMS-TS rate relative to SARS-CoV-2 infections during the Delta wave is unlikely to be explained by population level immunity from prior infection or vaccination. It is most likely due to viral mutations in key antigenic epitopes responsible for triggering the hyperinflammatory response observed with PIMS-TS.
Paediatric Inflammatory Multisystem Syndrome (PIMS-TS, also known as MIS-C) is a post-infectious acute inflammatory disorder, sharing features of both Kawasaki disease and toxic-shock syndrome, which typically occurs 2-6 weeks after exposure to SARS-CoV-2, mainly in children and young people (CYP). First described in London in April 2020, it is now widely reported worldwide. Early estimates suggested a risk of PIMS-TS of 1 in 3-4000 infected children. Whether this risk is sustained with new SARS-CoV-2 variants remains unknown. We utilised prospective data from the NHS South Thames Paediatric Network (STPN), which manages all cases of PIMS-TS amongst 1.5 million children in South-East England, to assess trends over time. All CYP aged 0–16 years with suspected PIMS-TS in the Network are discussed in a daily multi-disciplinary meeting, with diagnosis made according to RCPCH criteria, unchanged since September 2020.

We compared PIMS-TS cases with two independent SARS-CoV-2 infection datasets. We used publicly available UK Health Security Agency 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. These were matched to STPN catchment, weighting cases to reflect child population distributions according to area population estimates from the Office for National Statistics (ONS). Since this dataset could potentially be biased by evolving changes in testing behaviour, we also compared PIMS-TS cases to community infection rates in 2-11 year olds, obtained from the ONS COVID-19 Infection Survey. This survey randomly selects individuals in private households for fortnightly PCR tests, deriving regional and national estimates of proportions infected in different age-groups. All three datasets were independently normalised to the peak of the Alpha wave (January 2021), allowing comparison with future waves, and plotted against time (Fig. 1). PIMS-TS cases were plotted 40 days prior to hospitalisation, allowing for the lag from SARS-CoV-2 infection to hospitalisation. This interval led to the closest parallel in rise of SARS-CoV-2 infection and PIMS-TS cases during the Alpha wave.
Compared with the Alpha wave, we found fewer cases of PIMS-TS relative to SARS-CoV-2 infections during both initial and subsequent Delta waves.

With the emergence of the Delta variant in April 2021, SARS-CoV-2 incidence increased during the second half of 2021 and into the Omicron wave in 2022. Although testing practices changed with twice-weekly home rapid-antigen testing for secondary school students (11–16-year-olds) since March 2021, the incidence closely matched ONS estimates of community infection rates for children, indicating that the observed increase in SARS-CoV-2 infections was real. Similar trends were also observed nationally with SARS-CoV-2 infections confirmed by PCR-only. During this period, the rise in PIMS-TS cases remained relatively modest, approximately doubling from August to December 2021, compared to a greater than five-fold increase in SARS-CoV-2 infections.

Our findings indicate PIMS-TS incidence relative to SARS-CoV-2 infection was lower during the Delta variant wave compared to Alpha. Since the risk of re-infection with the Alpha or Delta variants was very low in children, most SARS-CoV-2 infections during Delta waves were likely to be first infections. Whilst COVID-19 vaccination has been shown to protect against PIMS-TS, it is unlikely to have contributed to reduced rates during the Delta wave, since vaccination of 12–15-year-olds only began in September 2021 and only achieved 21% uptake in London by mid-November 2021, while 5–11 year-olds remained unvaccinated.

We find that the lower PIMS-TS rate relative to SARS-CoV-2 infections during the Delta wave is unlikely to be explained by population level immunity from prior infection or vaccination in CYP, but could be due to viral mutations in key antigenic epitopes responsible for triggering the hyperinflammatory response observed with PIMS-TS. Currently, many children are being infected with Omicron including reinfection after prior infection with Alpha or Delta variants. The relative contributions of host immunity and viral changes to PIMS-TS rates relative to Omicron infections is obscured by increasing vaccination rates in UK children. Similar to Kawasaki disease which is also thought to have an infectious trigger, as more children become immune through natural SARS-CoV-2
infection or vaccination, we predict that PIMS-TS will become a sporadic disease occurring mainly in immunologically-naïve infants and toddlers.
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Conflict of Interest

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

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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.
Date of SARS-CoV-2 infection

Asymptomatic testing in schools

- PIMS-TS cases (admitted 40 days later)
  (STPN data, 0-14 years, STPN catchment)
- Reported SARS CoV-2 cases
  (UKHSA data, 0-14 years, STPN catchment)
- Estimated SARS-CoV-2 positivity
  (ONS data, 2-11 years, England)

Relative number of cases
(relative to peak of Alpha wave)