Supplementary Online Content

Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. Incidence rates and clinical outcomes of SARS-CoV-2 infection with the Omicron and Delta variants in children younger than 5 years in the US. *JAMA Pediatr*. Published online April 1, 2022. doi:10.1001/jamapediatrics.2022.0945

eMethods. TriNetX Database and Statistical Analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. TriNetX Database and Statistical Analysis

Description of TriNetX database

The data used in this study was collected on February 8, 2022 from the TriNetX COVID-19 Research Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 90 million patients from 66 healthcare organizations. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. MetroHealth System, Cleveland, Ohio, IRB has determined any research using TriNetX, is not Human Subject Research and therefore exempt from IRB review.

TriNetX is a platform that de-identifies and aggregates electronic health record (EHR) data from 66 contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations, across 50 states in the US. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care, and specialty treatment providers, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types including various commercial insurances, governmental insurance (Medicare and Medicaid), self-pay/uninsured, worker compensation insurance, military/VA insurance among others.

Self-reported race and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: (1) Race: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race; and (2) Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity.

Statistical analysis

Monthly incidence rates of first time SARS-CoV-2 infections (new cases per 1,000 persons per day) between September 2021 and January 2022 were examined in children under 5 years old, age 0-2 years and 3-4 years old. This time period included Delta predominance period (9/2021-11/2021), Omicron emergence period (12/1/2021-12/15/2021), and Omicron predominance period (12/16/2021-1/31/2022). In this study, incidence is a rate of first-time COVID-19 cases in children under 5 years old under analysis. For a given time window (each month in this study), the incidence proportion denominator includes all and only those children in the cohort under analysis, whose fact record overlaps the time window by at least one day and who did not contract COVID-19 any time before the time window. The incidence proportion numerator includes all and only those children who are in the denominator and who contracted COVID-19 within the time window. The monthly incidence rate denominator is the product of the number of children in the incidence proportion denominator and the number of days covered by each month. The incidence rate numerator is equivalent to the incidence proportion numerator.

We then tested whether severe clinical outcomes among children differed between Omicron and Delta cohorts and between Delta-2 and Delta cohorts. Cohorts were first propensity-score matched (1:1 using a nearest neighbor greedy matching with a caliper of 0.25 times the standard deviation) for demographics and comorbidities. Risk of death, ED visits, hospitalizations, ICU admissions and need for mechanical ventilation within 14 days following initial SARS-CoV-2 infection was compared between matched Omicron and Delta cohorts and between matched Delta-2 and Delta cohorts with hazard ratios and 95% confidence intervals. Kaplan-Meier analysis was used to estimate the probability of clinical outcomes. Cox's proportional hazards model was used to compare the two matched cohorts. The proportional hazard assumption was tested using the generalized Schoenfeld approach. The TriNetX Platform calculates the hazard ratios and associated confidence intervals, using R's Survival package v3.2-3. For generating hazard ratios, TriNetX sets robust=FALSE using the R survival package, which is a limitation of the TriNetX platform since it does not take into account potential clustering of COVID-19 cases within the healthcare organizations or specific geolocations.

Additional supplemental data is available at: http://nlp.case.edu/public/data/omicron-children-JAMAPed-online-data.docx