

Severe Pediatric COVID-19 and Multisystem Inflammatory Syndrome in Children From Wild-type to Population Immunity

A Prospective Multicenter Cohort Study With Real-time Reporting

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Background: SARS-CoV-2 variant evolution and increasing immunity altered the impact of pediatric SARS-CoV-2 infection. Public health decision-making relies on accurate and timely reporting of clinical data.

Methods: This international hospital-based multicenter, prospective cohort study with real-time reporting was active from March 2020 to December 2022. We evaluated longitudinal incident rates and risk factors for disease severity.

Results: We included 564 hospitalized children with acute COVID-19 (n = 375) or multisystem inflammatory syndrome in children (n = 189) from the Netherlands, Curaçao and Surinam. In COVID-19, 134/375 patients (36%) needed supplemental oxygen therapy and 35 (9.3%) required intensive care treatment. Age above 12 years and preexisting pulmonary conditions were predictors for severe COVID-19. During omicron, hospitalized children had milder disease. During population immunity, the incidence rate of pediatric COVID-19 infection declined for older children but was stable for children below 1 year. The incidence rate of multisystem inflammatory syndrome in children was highest during the delta wave and has decreased rapidly since omicron emerged. Real-time reporting of our data impacted national pediatric SARS-CoV-2 vaccination- and booster-policies.

Conclusions: Our data supports the notion that similar to adults, prior immunity protects against severe sequelae of SARS-CoV-2 infections in children. Real-time reporting of accurate and high-quality data is feasible and impacts clinical and public health decision-making. The reporting framework of our consortium is readily accessible for future SARS-CoV-2 waves and other emerging infections.

Key Words: COVID-19, SARS-CoV-2, MIS-C, pediatrics, real-time reporting (*Pediatr Infect Dis J* 2023;42:1077–1085)

Most SARS-CoV-2 infections in children are mild or asymptomatic. However, severe pediatric COVID-19 can occur, predominantly in children with preexisting chronic conditions.^{1–3} In addition, SARS-CoV-2 infected children sometimes develop the severe hyperinflammatory postinfectious condition multisystem inflammatory syndrome in children (MIS-C).^{4,5} The emergence

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The authors have no conflicts of interest to disclose.

Some of the data presented here is also shown on our study website www.covid-kids.nl. A modified version of the abstract was submitted to the European

Society of Pediatric Infectious Diseases (ESPID) and was accepted for an oral presentation at the ESPID 2023 congress in Lisbon. An online preprint version of the manuscript was posted on the SSRN website (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4401713).

The study is listed in the Health-RI COVID-19 data portal, in which federated metadata is deposited (<https://covid19initiatives.health-ri.nl/p/Project/27866022694505020>). Data will be shared with researchers who provide a methodologically sound proposal. Shared data can be used to achieve aims in the approved proposal. Only anonymous data will be shared. Proposals should be directed to e.p.buddingh@lumc.nl; to gain access, data requestors will need to sign a data access agreement. Supplementary code used for the real-time reporting framework will be deposited upon acceptance on: <https://github.com/AJTULLING-LUMC/Real-time-reporting-framework>. The code can also be provided upon request of the editor or reviewer.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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of the SARS-CoV-2 omicron variant was associated with reduced severity of COVID-19 in both adults and children, possibly related to prior immunity.^{6,7} Less is known about the current phase of population immunity and the impact on severe pediatric COVID-19 and MIS-C.⁸

Several online dashboards tracking SARS-CoV-2 infections and COVID-19 hospital admissions were available during the course of the pandemic. However, these systems lacked detail on the clinical features, risk factors and outcome of pediatric cases.^{9–12} At the start of the pandemic, we initiated a nationwide hospital-based multicenter, prospective cohort study with online real-time reporting and analyses to continuously track the features, risk factors and outcomes of severe pediatric acute COVID-19 and MIS-C throughout the different phases of the pandemic. Collected data was reported real-time on the study website (www.covidkids.nl).

Our aim was to provide clinicians and public health officials with real-time and freely accessible data on MIS-C and severe pediatric COVID-19, supporting clinical management and public health decisions. Here, we report the dynamics of the incidence rate and severity of pediatric acute COVID-19 and MIS-C throughout the pandemic, from wild-type to population immunity, comparing older children to infants without prior immunity. In addition, we describe the risk factors and extensive cross-sectional and longitudinal features of hospitalized pediatric patients with severe manifestations of SARS-CoV-2 infection.

MATERIALS AND METHODS

Study Design, Setting and Participants

This multicenter, prospective cohort study included patients from March 2020 to January 1 2023. All 7 academic hospitals in the Netherlands, 31/61 general hospitals, The National Center for Pediatric Oncology and 2 Caribbean hospitals (Surinam and Curaçao) included patients. Inclusion criteria were: children until the age of 18 years presenting to hospital with acute COVID-19 (polymerase chain reaction [PCR] and/or rapid antigen test), or with MIS-C. Informed consent and written approval were obtained from all parents (and children older than 12 years). The study was evaluated and approved by the local medical regional ethics committee (METC-LDD, reference number N20.043 and NL76177.058.21, protocols on the study website www.covidkids.nl). Case details were entered into an electronic data capture system. Real-time reporting and analyses were done using an automated R script (<https://github.com/AJTULLING-LUMC/Real-time-reporting-framework>) (Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/F236>). Analyses, tables and figures were exported daily to the study website (www.covidkids.nl/scientific-dashboard). Children with a coincidental finding of SARS-CoV-2 infection, who were not admitted to the hospital, or who had a clinical suspicion of MIS-C without meeting the WHO criteria, were excluded from further analyses.¹³ The STROBE reporting guidelines were followed (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/F237>).¹⁴

Data Collection

Data were collected using Castor Electronic Data Capture.¹⁵ Data collected included general patient characteristics (age, sex, body mass index¹⁶ and medical history), SARS-CoV-2 laboratory results (PCR/rapid antigen test/serology), laboratory markers (including estimated glomerular filtration rate¹⁷), presenting symptoms, vital signs (transformed to z scores^{18,19}), treatment, complications and outcome. The Centers for Disease Control and Prevention criteria were used to define organ involvement in MIS-C.⁹ Abnormal neurocognitive developmental mainly involved patients with developmental delay related

to severe underlying conditions (eg, metabolic disease, psychomotor retardation or genetic abnormality).

Outcomes

The primary outcome was the incidence rate ratio (IRR) and severity of pediatric COVID-19 and MIS-C in subsequent pandemic phases. For acute pediatric COVID-19, severe disease was defined as the need for supplemental oxygen therapy, and/or intensive care unit (ICU) admission.²⁰ For MIS-C, severe disease was defined as needing inotropics and/or invasive ventilatory support.

Secondary outcomes were the length of hospital stay between SARS-CoV-2 variants, age groups and disease severity. We compared laboratory markers at the initial hospital visit between mild and severe cases. We evaluated if adding systemic corticosteroids to intravenous immunoglobulin (IVIG) influenced the recovery of MIS-C, as determined by reduction in C-reactive protein (CRP) level, normalization of body temperature and length of hospital stay.

SARS-CoV-2 Variants and Population Immunity

Since data on SARS-CoV-2 variants were not available for individual cases, we used data from the Dutch National Institute for Public Health and the Environment (RIVM) to determine which SARS-CoV-2 variant was dominant (>80% of all SARS-CoV-2 infections) at any given timepoint.²¹ For MIS-C, we used a lag period of 3 weeks, since MIS-C is a postinfectious syndrome. The wild-type variant of SARS-CoV-2 was dominant prior to March 1, 2021; the alpha variant from March 1, 2021 to July 5, 2021; the delta variant from July 6, 2021 to January 2, 2022 and the omicron variant since January 3, 2022. Based on SARS-CoV-2 seroprevalence data, and the high efficacy of vaccine- or infection-induced humoral protection,^{22–24} in children in the Netherlands, the United Kingdom and globally, we extrapolated that population immunity in children was reached after the BA.2 omicron wave in July 2022.^{25–27} At that time, almost all Dutch children >12 years had neutralizing antibodies against SARS-CoV-2, compared to ~75% of 3-year-old children and ~50% of 1-year-old children. To explore if incidence rate and severity differed in children who were less likely to have been previously infected with SARS-CoV-2, we stratified the COVID-19 cohort in children younger and older than 1 year of age.

Statistical Analysis

Descriptive values are reported with numerator and denominator for categorical values, and median and interquartile ranges for continuous values. Statistical analyses were performed using R software (version 4.1.3). To determine risk factors of disease severity, a univariate logistic regression was performed. Subsequent multivariate analyses were done by including all variables that were univariately associated, with an uncorrected $P < 0.10$. The incidence rates were calculated per 1,000,000 pediatric person months for the different SARS-CoV-2 variant phases and adjusted for study coverage.

Incidence rates were calculated using the MIS-C and COVID-19 cases throughout the pandemic. Patients from the 2 Caribbean regions were excluded from this analysis. We corrected the incidence rates for study coverage, by determining the proportion of Dutch children living within the catchment area of hospitals participating in our study as compared to children living in the catchment area of nonparticipating hospitals (using Dutch Central Bureau for Statistics data on pediatric inhabitants per region).²⁸ The overall study coverage of pediatric COVID-19 hospital admissions was 56.2% of the Dutch pediatric population (Figure, Supplemental Digital Content 3, <http://links.lww.com/INF/F238>). For MIS-C,

coverage of 100% was assumed because all Dutch pediatric tertiary referral centers (including all pediatric ICUs) participated in the study. Confidence intervals (CIs) for incidence rates were calculated using the Poisson test. A univariate Poisson regression model was used to calculate the IRR per SARS-CoV-2 variant for pediatric COVID-19 hospital admissions and MIS-C. Since MIS-C is a postinfectious syndrome, which only occurs when the virus circulates, we also adjusted the IRR of MIS-C for pediatric COVID-19 hospitalizations in the same period.

To compare outcomes of different treatment regimens in MIS-C, a univariate logistic regression model, and a multivariate model with correction for disease severity, were used. To estimate the decline of CRP and body temperature over time during the MIS-C disease course, we used a generalized additive mixed model using the individual patients as a random effect. To visualize differences in laboratory markers at the initial hospital visit, we performed multiple Wilcoxon rank sum tests. Other statistical tests used in this article include the Fisher exact test and χ^2 test. All *P* values in the main- and supplementary material, were corrected using the Benjamini–Hochberg procedure. Corrected *P* < 0.05 was considered statistically significant.

RESULTS

Clinical Cohort Characteristics

During the study period, 650 patients were included in the study. Children not admitted because of COVID-19 and children not

meeting WHO criteria for MIS-C were excluded for further analysis (Figure, Supplemental Digital Content 4, <http://links.lww.com/INF/F239>). Data from 564 children were analyzed (189 patients with MIS-C and 375 patients with COVID-19). The dynamics of COVID-19-related pediatric hospital admissions mirrored Dutch adult hospitalizations, while MIS-C admissions lagged a few weeks behind (Fig. 1A). There were no regional differences in inclusions (Fig. 1B). Most cases were included when the wild-type variant was dominant (34%), followed by the delta variant (25%) (Table, Supplemental Digital Content 5, <http://links.lww.com/INF/F240>). Most children admitted because of COVID-19 (239/375, 64%) had a respiratory tract infection. About a third of admitted children (136/375, 36%) had predominantly nonrespiratory symptoms related to SARS-CoV-2 infection (eg, fever and/or gastrointestinal symptoms).

One patient was completely vaccinated, 2 were incompletely vaccinated and 6 had a documented prior SARS-CoV-2 infection (Table, Supplemental Digital Content 5, <http://links.lww.com/INF/F240>). Three MIS-C cases were incompletely vaccinated, and none were completely vaccinated. There were no documented cases of MIS-C after SARS-CoV-2 reinfection.

Severe disease, defined as a necessity for oxygen supplementation and/or ICU admission, occurred in 134/375 (36%) of COVID-19 patients (Table, Supplemental Digital Content 5, <http://links.lww.com/INF/F240>). Of these, 35/134 (26%) were admitted to ICU; 15 received mechanical ventilatory support; 7 required inotropic drug administration; 2 needed ECMO support and 1 patient with severe

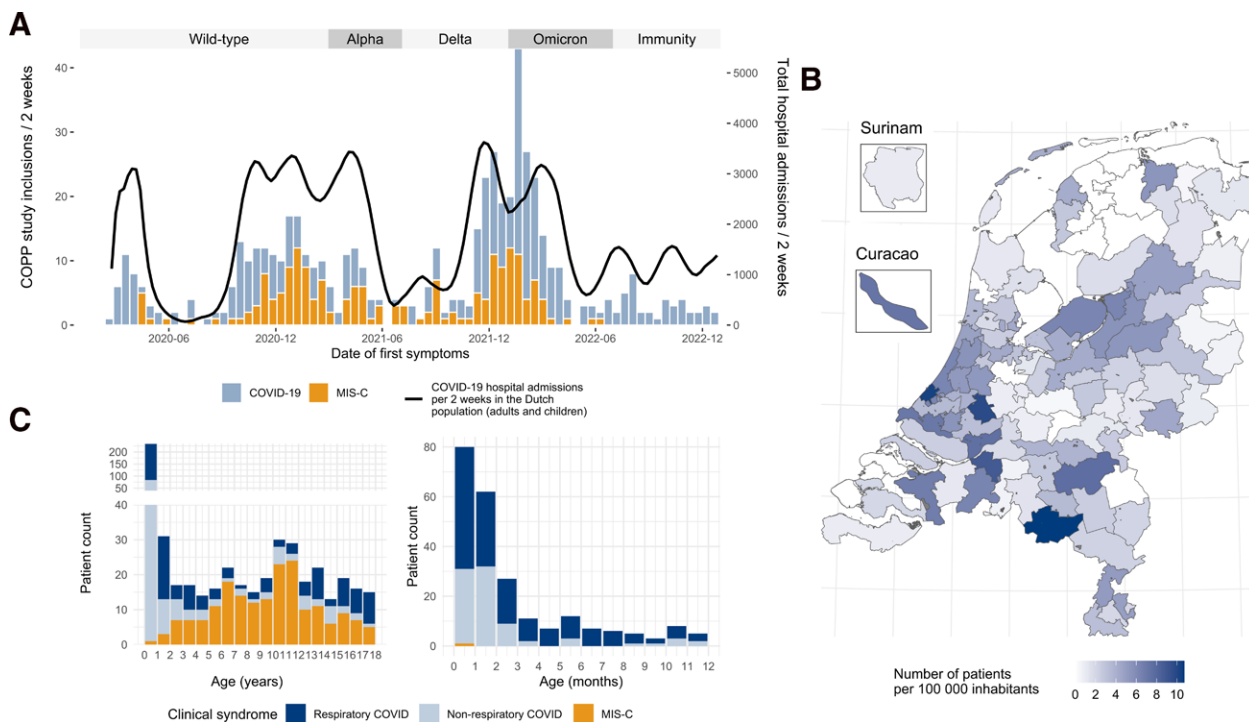


FIGURE 1. Summary panel of real-time reporting. Epidemiologic and demographic characteristics of the study cohort, as presented on the online dashboard. A: Date of first symptoms in patients with COVID-19 (blue) and MIS-C (orange). The black line shows overall (children and adults) national SARS-CoV-2 positive hospital admissions. Dominant SARS-CoV-2 variants (>80% of infections) are shown in the upper band. B: Geographical distribution of patients per 100,000 inhabitants in the Netherlands, Curaçao and Surinam. The Caribbean countries are not depicted to scale. C: Age distribution of study cohort. Patients with “Respiratory COVID-19” had predominantly respiratory symptoms at presentation. Patients with “Nonrespiratory COVID-19” had predominantly nonspecific symptoms at presentation, such as isolated fever or gastrointestinal complaints. Left pane: 0–18 years of age. Right pane: 0–12 months of age.

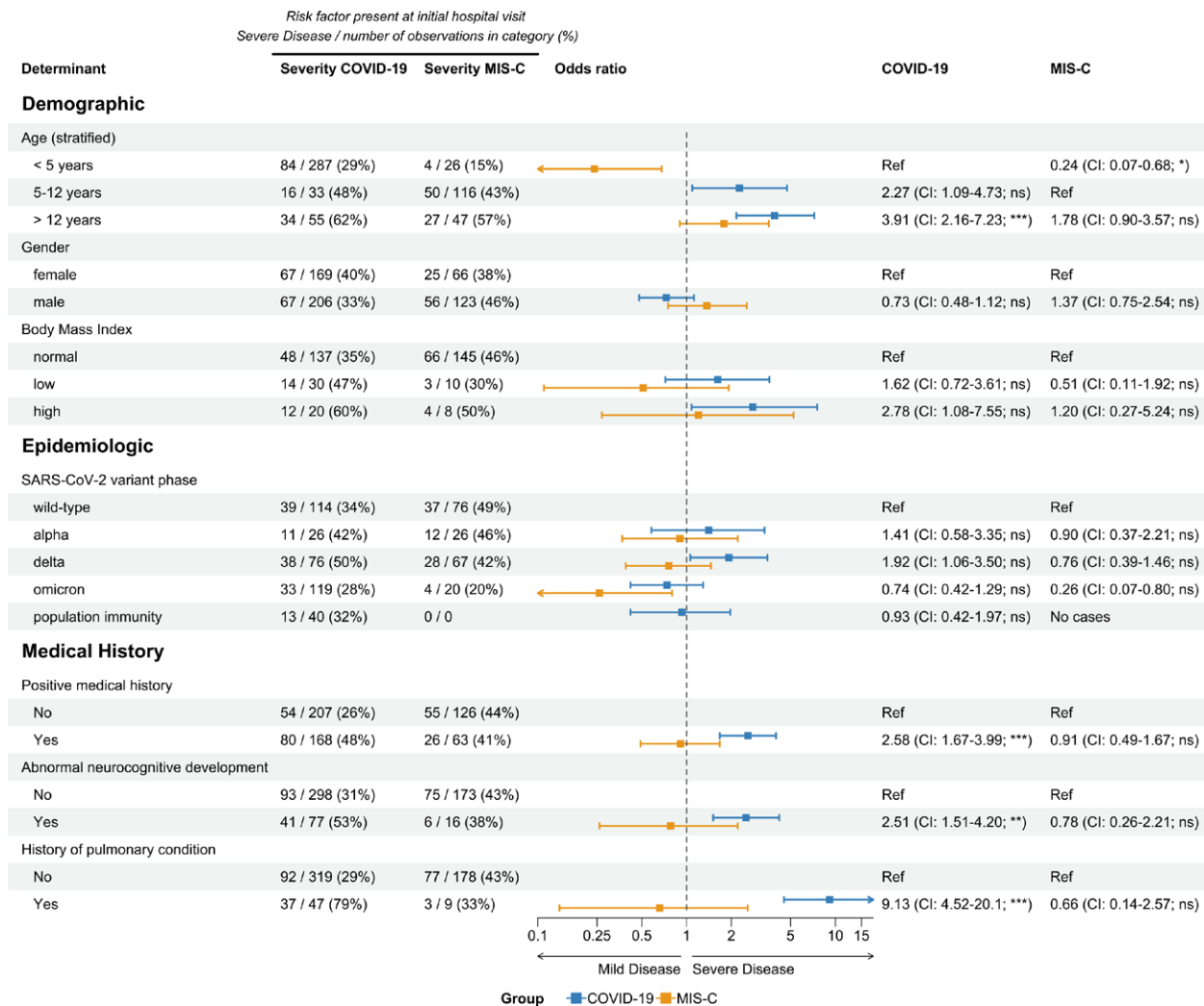


FIGURE 2. Risk factors of severe disease in COVID-19 and MIS-C. Demographic, epidemiologic and clinical characteristics of children admitted with COVID-19 or MIS-C. Results from a univariate logistic regression model, with disease severity as a dependent variable, are presented in the forest plot, with corresponding odds ratio, confidence intervals and *P* value. Proportions of severe cases over all observations in that group are shown with counts and percentages. *P* values were corrected using the Benjamini–Hochberg procedure (*P* values: ≥ 0.05 ns, $< 0.05^*$, $< 0.01^{**}$, $< 0.001^{***}$). CI indicates confidence interval; MIS-C, multisystem inflammatory syndrome in children.

Content 9, <http://links.lww.com/INF/F244>). In MIS-C, high respiratory and cardiac rate, low blood pressure and high inflammatory biomarkers (CRP and ferritin), lymphocytopenia, elevated cardiac biomarkers (NT Pro-BNP and troponin T), and reduced estimated glomerular filtration rate at admission were associated with severe disease (Figure, Supplemental Digital Content 9, <http://links.lww.com/INF/F244>). Cardiac and renal organ system involvement were predictors for severe MIS-C (Table, Supplemental Digital Content 10, <http://links.lww.com/INF/F245>). Positive SARS-CoV-2 PCR in nasopharyngeal swab at diagnosis of MIS-C was not a predictor for severe MIS-C (Table, Supplemental Digital Content 10, <http://links.lww.com/INF/F245>).

Dynamics of Disease Severity Over Time

To evaluate if there was a difference in severity and risk factors of COVID-19 in children younger than 1 year of age (who

are presumed to be more likely SARS-CoV-2 naive) as compared to older children (who, as the pandemic progressed, may have had prior SARS-CoV-2 exposure), we stratified our cohort by age below or above 1 year. For children younger than 1 year, length of hospital stay, proportion with severe disease and proportion needing ICU care was stable throughout the pandemic (Fig. 3 and Table, Supplemental Digital Content 11, <http://links.lww.com/INF/F246>). For children older than 1 year of age, there was less frequent severe disease (38% vs. 60%, $P = 0.03$) after omicron emerged and a significant reduction in length of hospital stay (median of 2 days vs. 3 days, $P = 0.005$) (Fig. 3 and Table, Supplemental Digital Content 12, <http://links.lww.com/INF/F247>).

For MIS-C, there was a trend for less severe disease during omicron as compared to earlier variants and a significantly reduced length of hospital stay (median of 4 days vs. 5 days, $P = 0.04$) (Fig. 3 and Table, Supplemental Digital Content 13, <http://links.lww.com/INF/F248>). Only 40 children were included with COVID-19 after

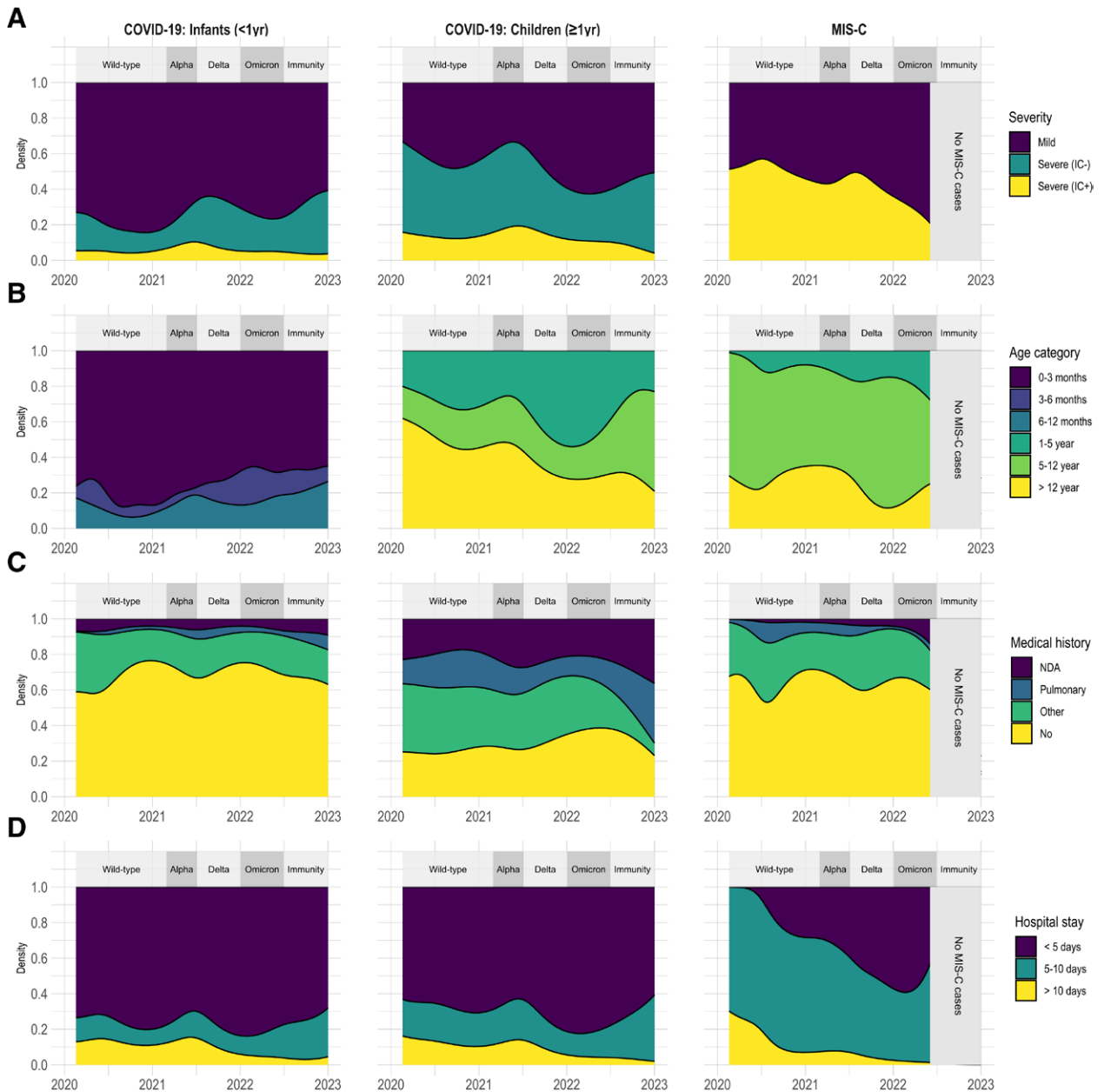


FIGURE 3. Patient dynamics throughout COVID-19 pandemic phases. Demographic and clinical characteristics of hospitalized COVID-19 and MIS-C patients during pandemic course by date of disease onset. Dominant SARS-CoV-2 variants (>80% of infections) are shown in the upper band. A: Disease severity. B: Age (stratified). C: Preexisting medical history. D: Hospital stay in days. IC indicates intensive care; MIS-C, multisystem inflammatory syndrome in children; NDA, neurocognitive developmental abnormalities.

July 2022, of whom only 6 were older than 1 year of age. Three of these were admitted because of an asthma exacerbation and 2 had prior severe neurocognitive developmental disorders.

Real-time Reporting and Public Health Impact

Daily updates on the dashboard on www.covidkids.nl provided the public, policymakers and physicians with real-time insight into the course of the pandemic in Dutch and Caribbean children. The National Health Council of the Netherlands referred to our dashboard on multiple occasions with regard to pediatric

vaccination policy (2021, 4 times), and booster vaccination for specific subgroups of children (2022–2023, 3 times, Table, Supplemental Digital Content 14, <http://links.lww.com/INF/F249>).

SARS-CoV-2 vaccination for children in the Netherlands was introduced in a stepwise approach, with the monovalent BioNTech/Pfizer vaccine. Children older than 12 years of age were eligible for vaccination from July 2021 onwards. The vaccination rate in this age group was 56%, which is reflected by a relative reduction in hospitalized teenagers since the autumn of 2021 (Fig. 3B).²⁹ Universal vaccination for children between 5 and 12 years of age

was offered in March 2022, but only 3% of children in this age group were vaccinated. Nevertheless, because of high circulation of the omicron variant in the spring of 2022, most children have developed immunity to SARS-CoV-2, regardless of vaccination.²⁵ In the last few months of our study, most hospitalized children were infants encountering the virus for the first time with a relatively mild disease course, and children with a history of pulmonary disease (and/or neurocognitive developmental disorder).

DISCUSSION

The COVID-19 pandemic has impacted social and health-care-related aspects of life on a global scale. Healthcare policy-makers, medical staff and hospital management depend on reliable and up-to-date information to guide decision-making. Since the start of the pandemic, Dutch pediatricians collected data on pediatric COVID-19 and MIS-C, in a concerted effort to determine the incidence and risk factors for a severe course. All clinical, demographic and epidemiological characteristics were continuously and automatically updated on an online dashboard. Here, we present the findings from this prospective cohort study.

Multiple COVID-19 dashboards have been set up globally, some of which also include pediatric patients, but none provided detailed clinical information on children of the present study.⁹⁻¹² Our real-time reporting facilitated monitoring of the magnitude, risk factors and outcome of pediatric COVID-19 and MIS-C. The analyses on our dashboard were of great interest to medical professionals and the general public. In addition, our data were instrumental to national SARS-CoV-2 vaccination policies in children.³⁰

In this study, we confirm that adolescents and children with abnormal neurocognitive development or preexisting pulmonary conditions are more likely to develop severe COVID-19.³¹ In line with previous studies, most children with MIS-C were previously healthy.³² Although this is not the first study to evaluate risk factors for severe disease in pediatric COVID-19 and MIS-C, it is unique in covering all sequential phases of the SARS-CoV-2 pandemic, from wild-type to population immunity.

In line with other studies,^{6,7} the SARS-CoV-2 omicron variant phase was associated with reduced severity. For adults, the reduced severity of omicron has been linked to increasing immunity as a result of natural infection and vaccination, but in children, this is less clear.³³

Incidence rates dropped dramatically during the course of the pandemic, both for children above 1 year of age admitted for COVID-19 and children with MIS-C. In contrast, incidence rate and severity remained stable through time for children younger than 1 year of age. These youngest children are not eligible for vaccination and are less likely to have been previously infected with SARS-CoV-2 than older children, and can therefore be presumed to lack protective immunity. In addition, infants (<1 year of age) very rarely develop reinfection with SARS-CoV-2 within the first year of life.²² Although a lower pathogenicity of SARS-CoV-2 omicron variant is not completely ruled out, this supports the notion that similar to adults, prior immunity protects against severe sequelae of SARS-CoV-2 infections in children.

Due to the observational nature of the study design, not all parameters were available for all patients, which may limit the generalizability of risk factor identification. Another limitation is, that because of ethical considerations, we did not collect data on ethnicity, which has been reported as a risk factor for MIS-C in multiple reports.^{5,34} Additionally, our study may be limited by inclusion biases. Informed consent may have been more difficult to obtain for deceased patients as well as for patients who were discharged shortly after presentation. Finally, there could be a reporting bias

towards more severe cases both at the individual study site level and at the study level, since all academic hospitals and pediatric ICUs participated in the study, accounting for the most severe COVID-19 cases and many MIS-C cases, and the majority -but not all- general hospitals included cases.

Currently, pediatric hospital admissions for severe SARS-CoV-2-related conditions are very rare, potentially due to a high degree of protective immunity in children. Should future SARS-CoV-2 variants or declining immunity result in an increased burden of disease, the reporting framework of our consortium is readily accessible. Other (re-)emerging pediatric infectious diseases also warrant a collaborative effort with real-time reporting of data. Therefore, our consortium is currently using this infrastructure to study the recent increase in invasive group A streptococcal infections in children.³⁵ Our study shows that real-time reporting of accurate and high-quality data is feasible and can be implemented rapidly in rare, life-threatening diseases, and impacts clinical and public health decision-making.

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ERRATUM

Intermittent Fevers and Inability to Bear Weight in a 7-Year-Old: ERRATUM

In the article “Intermittent Fevers and Inability to Bear Weight in a 7-Year-Old”¹ that appeared on pages 85-86 of the January 2021 issue of *The Pediatric Infectious Disease Journal*, two author names were missing. The names of the missing authors are Dr. Sandra Isabel and Dr. Ari Bitnun. Dr. Sandra Isabel should have been #4 in the author list and Dr. Ari Bitnun should have been #5 in the author list.

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