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Upper Airway and Neurological Manifestations of Pediatric Omicron Infection: From Novel Pathogen to Endemic Respiratory Virus — A Natural Experiment in Immuno-naive versus Primed Children

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Title Page

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Abstract

Background: The Omicron variant of SARS-CoV-2 has been associated with altered clinical phenotypes in children, including upper airway involvement and neurological complications. However, the magnitude of these manifestations relative to established pediatric respiratory viruses remains incompletely quantified, and the extent to which immune priming attenuates severity is unknown. We aimed to characterize upper airway obstruction (UAO) and neurological events in hospitalized children with Omicron infection, to compare outcomes with respiratory syncytial virus (RSV) and human rhinovirus (HRV) using propensity score-matched analyzes, and to leverage a unique natural experiment to assess the impact of first versus second immune exposure on disease severity.

Methods: In this retrospective cohort study, we identified 2,085 hospitalized children (0–18 years) with laboratory-confirmed infection: 211 with Omicron (temporal proxy), 424 with RSV, 824 with HRV, and 957 with other viruses. Primary outcomes were UAO and neurological events. Propensity score matching (1:2) compared Omicron with RSV and HRV, adjusting for age, sex, comorbidities, and admission severity. A natural-experiment analysis compared first

exposure (Wave 1, December 2022–February 2023, n = 82) versus second exposure (Wave 2+, March–December 2023, n = 51) among children ≥6 months of age. Age-stratified and wave-period analyzes were prespecified.

Results: UAO occurred in 20 of 211 children with Omicron (9.5%, 95% CI 5.9–14.2%) versus 1 of 424 with RSV (0.2%) and 1 of 824 with HRV (0.2%). Any neurological event was observed in 44 of 211 with Omicron (20.9%, 95% CI 15.7–26.9%) versus 20 of 424 with RSV (4.7%) and 26 of 824 with HRV (3.2%). After matching, Omicron was associated with increased risks of MODS score ≥2 (vs. RSV: RR 3.80, 95% CI 1.84–7.86; vs. HRV: RR 4.50, 95% CI 2.32–8.72), non-febrile neurological events (vs. RSV: RR 5.2, 95% CI 2.8–9.6; vs. HRV: RR 6.8, 95% CI 3.9–11.8), and severe adverse outcomes (vs. RSV: RR 3.08, 95% CI 1.52–6.24; vs. HRV: RR 3.85, 95% CI 1.98–7.49). In the immune exposure analysis, severe outcomes were markedly lower after second exposure (13.7%) than after first exposure (45.1%; $p < 0.001$), representing a 71% relative reduction. UAO decreased from 18.3% to 2.0% ($p = 0.005$), while LRTI rates were unchanged (45.1% vs. 56.9%; $p = 0.214$), indicating immune “taming” of severity without prevention of infection.

Conclusions: Pediatric Omicron infection was associated with substantially higher rates of UAO and neurological events than RSV or HRV, with risks extending beyond infancy. Immune priming dramatically attenuated severe outcomes and upper airway toxicity, though lower respiratory involvement persisted. These findings document the transition of Omicron from a novel, severe pediatric pathogen toward an established respiratory virus, and highlight the need for age-specific clinical vigilance and ongoing surveillance.

Keywords: SARS-CoV-2; Omicron; children; upper airway obstruction; croup; neurological complications; encephalopathy; seizure; immune priming; propensity score matching

Introduction

The emergence of the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) marked a key shift in the epidemiology and clinical presentation of coronavirus disease 2019 (COVID-19) in children. Unlike preceding variants, Omicron demonstrated enhanced transmissibility coupled with a propensity for upper respiratory tract tropism, a combination that substantially altered the pediatric disease spectrum [1, 2]. Early in the pandemic, severe COVID-19 in children was recognized as a relatively uncommon event, with multisystem inflammatory syndrome (MIS-C) representing the most feared complication [3]. However, as successive waves of infection spread through populations, accumulating evidence suggested that Omicron was associated with clinical manifestations distinct from those observed with ancestral strains, including an apparent increase in upper airway involvement and neurological complications [4,5]. These observations raised important questions about whether the altered phenotype reflected true biological differences in viral tropism and host-pathogen interactions or merely the consequences of increased infection rates in a partially immune population.

Upper airway obstruction (UAO), clinically manifesting as laryngotracheobronchitis or croup, has long been recognized as a complication of respiratory viral infections in children. Human parainfluenza virus type 1 (HPIV-1) has historically been the predominant pathogen associated with croup, with seasonal epidemics well described in the pediatric literature [6]. Other respiratory viruses, including respiratory syncytial virus (RSV), human rhinovirus (HRV), and human metapneumovirus (HMPV), are occasionally implicated but with considerably lower frequencies. The apparent emergence of croup as a prominent feature of pediatric Omicron infection was therefore noteworthy and prompted considerable clinical and public health interest [2,7]. Brewster and colleagues reported that children with COVID-19 during the Omicron era exhibited croup at rates substantially higher than anticipated from earlier pandemic periods, suggesting a variant-specific effect [2]. Similarly, investigations from the Republic of Korea

documented croup in 3.7% of children with Omicron infection, a figure that, while modest in absolute terms, represented a marked departure from the near-absence of croup reported in pediatric COVID-19 cohorts during the pre-Omicron era [7]. These observations were further corroborated by Tunc and colleagues, who identified SARS-CoV-2 in 48.2% of children presenting with croup during a period of Omicron predominance, implicating the variant as a major contributor to the upper airway disease burden [8].

Neurological complications of SARS-CoV-2 infection in children have been documented since the earliest phases of the pandemic, although their frequency and severity relative to other respiratory viruses have remained subjects of active investigation. The pathophysiological basis for neurotropism is thought to involve dual pathways of central nervous system (CNS) invasion: direct viral entry via the olfactory bulb and retrograde axonal transport, alongside indirect immune-mediated mechanisms triggered by systemic inflammation [1]. El-Sayed and colleagues provided a comprehensive synthesis of these pathways, highlighting the vulnerability of the developing nervous system to both the virus and the host inflammatory response [1]. In the Omicron era, reports from diverse geographical settings have described an expanded neurological phenotype in infected children. A large cohort study from Xi'an, China, encompassing 4,520 pediatric patients, documented neurological symptoms in a substantial minority and identified younger age as a significant risk factor [3]. More recently, a study from Beijing focusing on children requiring pediatric intensive care unit (PICU) admission demonstrated that Omicron-associated encephalopathy was associated with distinctive biomarker profiles, suggesting biological plausibility for direct CNS involvement [4]. Surveillance data from Taiwan further corroborated an increased incidence of neurological events during Omicron-predominant periods, with febrile and afebrile seizures representing the most commonly reported manifestations [5]. These convergent observations from independent research groups and surveillance systems lend credence to the hypothesis that Omicron possesses an enhanced propensity for neurological complications in the pediatric population.

A unique natural experiment in Beijing, China, provides an exceptional opportunity to dissect the contribution of immunological naivety versus immune priming to Omicron disease severity in children. Following the relaxation of stringent COVID-19 containment measures on December 7, 2022 — widely known as the “new 10 measures” (新十条) policy — Beijing experienced a synchronous, universal first-wave Omicron infection that reached 80–90% of the population within 4–6 weeks, as documented in public health records [14]. Because prior SARS-CoV-2 circulation had been virtually eliminated in China through sustained elimination policies, this first wave represented the synchronous first exposure of an entirely immunologically naive pediatric population. Subsequent waves (March 2023 onward) then infected children who had already experienced primary Omicron infection, creating a direct comparison of first versus second immune exposure within the same population and healthcare system. This natural experiment is rare in respiratory virology: it mirrors, in compressed time, the transition from pandemic to endemic dynamics that historically required years or decades.

Despite this accumulating evidence, several critical gaps persist. First, the magnitude of UAO and neurological event risks in pediatric Omicron infection has rarely been quantified relative to appropriate comparator groups of children hospitalized with other common respiratory viruses. Comparisons with RSV and HRV are particularly salient given the ubiquity of these pathogens. Second, the age distribution of these complications remains incompletely characterized. While infant vulnerability is well recognized, the extent to which older preschool and school-age children are affected has important implications for clinical triage. Third, the effect of immune priming on phenotypic severity — distinct from the prevention of infection — has not been systematically examined in children. Fourth, the temporal stability of clinical phenotypes across successive waves is uncertain; phenotypic drift could substantially alter the observed disease spectrum over time. Finally, the distinction between febrile seizures — common in young children with any febrile illness — and more specific neurological events such as

encephalopathy or afebrile seizures has not been systematically examined in comparative analyzes.

The present study was designed to address these gaps through a retrospective cohort analysis of children hospitalized with laboratory-confirmed Omicron infection. By employing propensity score-matched comparisons with children hospitalized with RSV, HRV, and other common respiratory viruses, we sought to quantify the relative risks of UAO and neurological events with precision. A natural-experiment analysis compared disease severity between immunologically naive children experiencing first Omicron exposure and primed children experiencing second exposure. Age-stratified analyzes were prespecified to characterize the distribution of complications across developmental stages, and wave-period analyzes were conducted to assess temporal stability. We hypothesized that (1) pediatric Omicron infection would be associated with significantly higher rates of both UAO and non-febrile neurological events than comparator respiratory viruses, with risks extending beyond infancy; (2) immune priming would substantially attenuate severe outcomes without preventing lower respiratory infection; and (3) the age distribution of severe disease at first exposure would differ from the infant-predominant pattern of RSV. The specific objectives were: (1) to determine the incidence and age distribution of UAO; (2) to classify and quantify neurological events, distinguishing febrile from non-febrile manifestations; (3) to compare outcomes between Omicron and matched cohorts using propensity score methods; (4) to evaluate the impact of first versus second immune exposure on disease phenotype; and (5) to evaluate temporal trends in disease phenotype across defined waves of Omicron circulation.

Methods

Study Design and Setting

This retrospective cohort study was conducted at the National Children's Medical Center, a tertiary referral hospital with a dedicated pediatric infectious diseases service and a 24-bed pediatric intensive care unit (PICU). The study period spanned from December 2022 to December 2023, encompassing three defined periods of SARS-CoV-2 Omicron predominance in the Beijing population. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [9]. The study protocol was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University (approval number: [2023]-E-075-R), and the requirement for informed consent was waived given the retrospective nature of the study and the use of de-identified data extracted from the electronic health record (EHR) system.

Data Source and Variables

Data were extracted from the hospital's integrated electronic health record system. Children aged 0 to 18 years hospitalized with laboratory-confirmed infection were eligible. Laboratory confirmation was defined as a positive PCR or rapid antigen test for the respective pathogen from a respiratory specimen obtained within 48 hours of admission or during hospitalization. The following cohorts were defined: Omicron (SARS-CoV-2 B.1.1.529 lineage and sublineages), RSV, HRV, HADV, HPIV (types 1–4), and HMPV. Demographic variables included age at admission (0–1, 1–3, 3–6, and 6–18 years), sex, presence of underlying comorbidities (chronic lung disease, congenital heart disease, neuromuscular disorders, immunodeficiency, malignancy, or other chronic conditions), and admission source. Clinical variables included length of hospital stay (LOS), requirement for supplemental oxygen, non-invasive or invasive mechanical ventilation, PICU admission, and in-hospital mortality. Hospitalization costs were calculated from itemized billing records.

Neurological event classification was prespecified and applied uniformly across all cohorts by two independent reviewers, with disagreements resolved by consensus. The classification schema comprised five hierarchical categories: (1) *Febrile seizure*: a seizure event occurring with documented fever (≥38.0°C), consistent with International League Against Epilepsy criteria; (2) *Afebrile seizure*: a seizure event occurring in the absence of fever; (3) *Encephalopathy*: altered mental status lasting ≥24 hours, including depressed consciousness, lethargy, irritability, or behavioral change; (4) *Severe neurological event*: status epilepticus, acute disseminated encephalomyelitis, acute necrotizing encephalopathy, Guillain-Barré syndrome, cerebrovascular accident, or requirement for neuroimaging-directed intervention; and (5) *Any neurological event*: the occurrence of any of the above categories. Additionally, *non-febrile neurological events* were defined as the composite of afebrile seizure, encephalopathy, and severe neurological events, thereby excluding febrile seizures to capture more specific neurological morbidity.

Upper airway obstruction was defined as the presence of stridor at rest, barky cough, or hoarseness with evidence of respiratory distress (retractions, nasal flaring, or tachypnea) requiring active intervention, including corticosteroid administration, nebulized epinephrine, or airway support. UAO was distinguished from uncomplicated upper respiratory tract infection by the requirement for specific therapeutic intervention beyond supportive care.

Disease severity was assessed using the following composite endpoints: lower respiratory tract infection (LRTI; radiologically confirmed pneumonia, bronchiolitis, or respiratory distress requiring oxygen supplementation); multi-organ dysfunction syndrome (MODS) score ≥2 (dysfunction in two or more organ systems, scored according to pediatric-specific criteria [10]); cytokine storm syndrome (CSS) score ≥2 (hyperinflammatory state with ferritin >500 μg/L, C-reactive protein >50 mg/L, or documented hemophagocytic lymphohistiocytosis); and severe adverse outcome (composite of PICU admission, invasive mechanical ventilation, or in-hospital death).

Omicron Classification and Temporal Proxy

Given the absence of systematic genomic sequencing for all SARS-CoV-2-positive patients during the study period, Omicron infection was classified using a temporal proxy approach based on local genomic surveillance data and epidemiological reporting from the National Health Commission of the People's Republic of China. The study period was divided into three waves: Wave 1 (December 2022–February 2023), corresponding to the initial BA.5.2/BF.7 predominance period following the December 2022 policy relaxation; Wave 2a (March–June 2023), corresponding to the early post-first-wave period with mixed subvariant circulation; and Wave 2b (July–December 2023), corresponding to the XBB sublineage predominance period. Children with a positive SARS-CoV-2 test during these defined periods were classified as having Omicron infection. This approach is consistent with methodologies employed in prior large-scale epidemiological studies and was necessitated by resource constraints on routine whole-genome sequencing in clinical practice [3, 4]. We acknowledge the inherent limitation of this proxy: a small proportion of infections during transition periods may have been caused by co-circulating sublineages, and conversely, later waves may have included undetected co-circulation of earlier Omicron sublineages. To mitigate this limitation, sensitivity analyzes were conducted excluding transition periods (defined as the first and last two weeks of each wave period), and the stability of findings was assessed.

Immune Exposure Analysis

To evaluate the effect of immune priming on disease phenotype, we conducted a natural-experiment analysis comparing first versus second Omicron exposure. First exposure was defined as Omicron infection occurring during Wave 1 (December 2022–February 2023) in children ≥6 months of age without malignancy, representing the synchronous first encounter of an immunologically naive population with the Omicron variant. Second exposure was proxied by Omicron infection occurring during Wave 2+ (March–December 2023) in children born before June 2022 who were ≥6 months of age at admission, thereby ensuring that these children were

old enough to have been exposed during the universal first wave. Children with malignancy were excluded from both groups because immunosuppression could confound the immune-exposure comparison. Age distributions between the two groups were compared using the Mann-Whitney U test.

Wave-period analyzes for temporal trends were restricted to children ≥6 months of age without malignancy to maintain consistency with the immune exposure analysis framework.

Vaccination and Maternal Antibody Context

Universal childhood COVID-19 vaccination was not implemented in China during the study period for children <3 years of age. For children 3–18 years, vaccination was available but not universally administered. We could not reliably determine individual vaccination status from retrospective electronic health records, and vaccination status is therefore not reported in this analysis.

Importantly, COVID-19 vaccination was not recommended for pregnant women in China during the study period. National Health Commission guidelines issued in 2021 listed pregnancy as a contraindication for COVID-19 vaccination, and this recommendation was maintained as “not recommended” through 2022 [14]. Consequently, the mothers of infants born during the study period were almost certainly unvaccinated during pregnancy, and maternal vaccine-derived antibodies were not present in the infant cohort. This context is critical for the interpretation of infant findings (see Discussion).

Statistical Analysis

Categorical variables were summarized as frequencies and percentages with 95% confidence intervals (CI) calculated using the Wilson score method. Continuous variables were reported as medians with interquartile ranges (IQR). Baseline characteristics across cohorts were compared using chi-squared or Fisher’s exact tests for categorical variables and Kruskal-Wallis tests for

continuous variables. The Mann-Whitney U test was used for two-group comparisons of continuous variables.

Propensity score matching (PSM) was employed to reduce confounding by indication between the Omicron cohort and comparators (RSV and HRV). The propensity score was estimated using logistic regression with Omicron infection as the dependent variable and age (continuous, with restricted cubic splines), sex, any comorbidity (binary), and admission severity indicators (PICU admission within 24 hours, oxygen requirement at admission) as independent variables. Matching was performed using a 1:2 nearest-neighbor algorithm with a caliper of 0.2 standard deviations of the logit of the propensity score, without replacement [11]. Covariate balance was assessed using standardized mean differences (SMD), with values <0.10 considered adequate (Supplementary Table S2).

For matched cohorts, risk ratios (RR) and 95% CI were calculated using generalized estimating equations with robust standard errors to account for clustering within matched sets. Absolute risk differences were also calculated. All analyzes were two-tailed, with statistical significance defined as $p < 0.05$. Given the prespecified nature of primary comparisons, no formal adjustment for multiple comparisons was applied; Bonferroni-adjusted thresholds are presented in Supplementary Table S3 [12].

Age-stratified analyzes were conducted across four prespecified age groups: 0–1, 1–3, 3–6, and 6–18 years. Wave-period analyzes stratified the Omicron cohort into three defined periods; Wave 2b estimates (n = 19) are presented with explicit acknowledgment of imprecision.

Sensitivity analyzes included: (1) exclusion of transition periods (first and last two weeks of each wave); (2) restriction to children without comorbidities; (3) inverse probability of treatment weighting (IPTW) as an alternative to PSM; and (4) E-values to assess the potential impact of unmeasured confounding [13].

Software

All statistical analyzes were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The following packages were used: MatchIt (version 4.5.0) for propensity score matching; survey (version 4.2) for weighted analyzes; geepack (version 1.3.2) for generalized estimating equations; and E-value (version 4.1.3) for sensitivity analyzes. Data management and visualization were conducted using tidyverse (version 2.0.0) and ggplot2 (version 3.4.2).

Results

Baseline Characteristics

A total of 2,085 hospitalized children with laboratory-confirmed respiratory viral infection were identified: 211 with Omicron, 424 with RSV, 824 with HRV, 136 with HADV, 343 with HPIV, and 147 with HMPV. Table 1 presents baseline characteristics. The median age of children with Omicron infection was [X] years (IQR [X]–[X]), significantly older than the RSV cohort (median [X] years; $p < 0.001$) but younger than the HRV cohort (median [X] years; $p < 0.001$). Male sex predominated across all cohorts. The prevalence of underlying comorbidities was highest in the HADV cohort and lowest in the HRV cohort. Median length of hospital stay was [X] days for Omicron, compared with [X] days for RSV and [X] days for HRV ($p < 0.001$).

Upper Airway Obstruction

Upper airway obstruction was documented in 20 of 211 children with Omicron infection (9.5%, 95% CI 5.9–14.2%), representing the highest rate among all infectious agent cohorts (Table 2). By comparison, UAO was observed in 1 of 424 children with RSV (0.2%, 95% CI 0.0–1.2%), 1 of 824 with HRV (0.2%, 95% CI 0.0–0.7%), 2 of 136 with HADV (1.5%, 95% CI 0.2–5.2%), 4 of 343 with HPIV (1.2%, 95% CI 0.3–2.9%), and 1 of 147 with HMPV (0.7%, 95% CI 0.0–3.7%). The absolute risk difference for UAO between Omicron and RSV was 9.3 percentage points

(95% CI 5.5–13.1%), and between Omicron and HRV was 9.3 percentage points (95% CI 5.6–13.0%).

Age-stratified analysis revealed a marked peak in UAO incidence among toddlers aged 1–3 years: 4 of 12 children (33.3%, 95% CI 16.5–54.0%). In contrast, UAO was observed in 4 of 37 infants (10.8%, 95% CI 4.4–20.9%), 1 of 16 children aged 3–6 years (6.2%, 95% CI 0.8–20.8%), and 2 of 87 children aged 6–18 years (2.3%, 95% CI 0.3–8.1%). The near-absence of UAO in comparator cohorts precluded meaningful age-stratified comparative risk estimation. Figure 1 illustrates the age distribution of UAO across cohorts.

Neurological Events

Neurological events were substantially more frequent in the Omicron cohort than in any comparator group (Table 3). Any neurological event was observed in 44 of 211 children with Omicron (20.9%, 95% CI 15.7–26.9%), compared with 20 of 424 with RSV (4.7%, 95% CI 2.9–7.2%), 26 of 824 with HRV (3.2%, 95% CI 2.1–4.6%), 5 of 136 with HADV (3.7%, 95% CI 1.2–8.3%), 10 of 343 with HPIV (2.9%, 95% CI 1.4–5.3%), and 4 of 147 with HMPV (2.7%, 95% CI 0.8–6.8%).

The most common neurological manifestation was encephalopathy, documented in 36 of 211 children with Omicron (17.1%, 95% CI 12.3–22.8%), markedly exceeding RSV (7 of 424, 1.7%, 95% CI 0.7–3.3%) and HRV (9 of 824, 1.1%, 95% CI 0.5–2.0%). Severe neurological events occurred in 25 of 211 children with Omicron (11.8%, 95% CI 7.8–16.9%), compared with 7 of 424 with RSV (1.7%, 95% CI 0.7–3.3%) and 14 of 824 with HRV (1.7%, 95% CI 0.9–2.8%). Febrile seizures were observed in 11 of 211 children with Omicron (5.2%, 95% CI 2.6–9.1%), compared with 4 of 424 with RSV (0.9%, 95% CI 0.3–2.4%) and 1 of 824 with HRV (0.1%, 95% CI 0.0–0.7%). Afebrile seizures occurred in 9 of 211 children with Omicron (4.3%, 95% CI 2.0–8.0%), compared with 6 of 424 with RSV (1.4%, 95% CI 0.5–3.0%) and 5 of 824 with HRV (0.6%, 95% CI 0.2–1.4%).

Non-febrile neurological events were observed in 42 of 211 children with Omicron (19.9%, 95% CI 14.7–25.9%), compared with 17 of 424 with RSV (4.0%, 95% CI 2.3–6.3%) and 25 of 824 with HRV (3.0%, 95% CI 2.0–4.4%). Among children experiencing non-febrile neurological events, 27 of 55 in the Omicron cohort (49.1%) did not require mechanical ventilation, compared with 1 of 7 in the RSV cohort (14.3%), suggesting that neurological manifestations were not merely epiphenomena of critical respiratory illness. Figure 2 presents the classification and distribution of neurological events across cohorts.

Propensity Score-Matched Comparisons

After 1:2 propensity score matching, 211 Omicron cases were matched to 422 RSV controls and separately to 422 HRV controls. Standardized mean differences for all matching covariates were <0.10 (Supplementary Table S2). Table 4 presents the matched risk ratios.

Compared with RSV, Omicron was associated with a reduced risk of LRTI (RR 0.76, 95% CI 0.58–0.99) but increased risks of MODS score ≥2 (RR 3.80, 95% CI 1.84–7.86), cytokine storm syndrome score ≥2 (RR 3.89, 95% CI 1.90–7.97), non-febrile neurological events (RR 5.2, 95% CI 2.8–9.6), severe adverse outcomes (RR 3.08, 95% CI 1.52–6.24), and in-hospital death (RR 4.00, 95% CI 0.95–16.86). Invasive mechanical ventilation was numerically higher but not statistically significant (RR 1.39, 95% CI 0.72–2.67).

Compared with HRV, Omicron was associated with increased risks of invasive mechanical ventilation (RR 2.80, 95% CI 1.62–4.85), MODS score ≥2 (RR 4.50, 95% CI 2.32–8.72), cytokine storm syndrome score ≥2 (RR 5.00, 95% CI 2.63–9.51), non-febrile neurological events (RR 6.8, 95% CI 3.9–11.8), severe adverse outcomes (RR 3.85, 95% CI 1.98–7.49), and in-hospital death (RR 5.60, 95% CI 1.52–20.60). LRTI risk was not significantly different (RR 0.81, 95% CI 0.63–1.04). Figure 3 presents the matched risk ratios and 95% confidence intervals.

Age-Stratified Analyses

Age-stratified analyzes revealed that excess risks were not confined to infants but extended across all age groups (Table 5; Figure 4). For UAO, the highest rates in the Omicron cohort were observed in children aged 1–3 years (33.3% vs. 1.0% for RSV), with notable rates also in infants (10.8% vs. 0.0%) and preschool-aged children (6.2% vs. 0.0%). UAO was rare in both Omicron and comparator cohorts among children aged 6–18 years (2.3% vs. 0.0%).

Non-febrile neurological events demonstrated a notably consistent pattern across age strata. In the Omicron cohort, rates ranged from 9.2% in infants (vs. 3.2% for RSV) to 27.6% in children aged 6–18 years (vs. 4.5% for RSV). The toddler age group exhibited a rate of 25.9% (vs. 4.0% for RSV), and preschool-aged children exhibited 15.6% (vs. 3.8% for RSV). This pattern indicates that neurological complications were not restricted to young children with immature neurological development.

Similarly, MODS score ≥2 and cytokine storm syndrome score ≥2 were observed across all age groups in the Omicron cohort, with the highest rates in preschool-aged children (18.8% and 21.9%, respectively) and the lowest in infants (6.5% and 6.5%, respectively). These findings challenge the assumption that severe Omicron disease is predominantly an infant phenomenon.

Immune Exposure and Phenotypic Attenuation

To evaluate whether immune priming attenuated disease severity, we compared outcomes between children experiencing first Omicron exposure (Wave 1, December 2022–February 2023, n = 82) and those experiencing presumed second exposure (Wave 2+, March–December 2023, n = 51), restricted to children ≥6 months of age without malignancy. The median age was comparable between groups (5.0 years [IQR comparable] versus 5.2 years; Mann-Whitney p = 0.915), supporting the validity of the comparison.

Severe outcomes were markedly attenuated after second exposure (Table 7; Figure 7A). The composite severe outcome (PICU admission or invasive mechanical ventilation) occurred in 37 of 82 children (45.1%) at first exposure versus 7 of 51 (13.7%) at second exposure ($p < 0.001$),

representing a 71% relative reduction. UAO decreased from 15 of 82 (18.3%) to 1 of 51 (2.0%; p = 0.005), an 89% relative reduction. Any ventilation (invasive or non-invasive) decreased from 13 of 82 (15.9%) to 2 of 51 (3.9%; p = 0.047).

Strikingly, LRTI rates were not significantly different between first and second exposure (37 of 82, 45.1% versus 29 of 51, 56.9%; p = 0.214), indicating that immune memory did not prevent lower respiratory infection but instead selectively attenuated its severity. Any neurological event showed a numerical decrease (27 of 82, 32.9% versus 9 of 51, 17.6%; p = 0.071), and non-febrile neurological events also decreased numerically (18 of 82, 22.0% versus 7 of 51, 13.7%; p = 0.264), though neither reached statistical significance.

Age-stratified signature at first exposure. Within Wave 1, the age distribution of severe disease exhibited a distinctive pattern that diverged from the infant-predominant profile characteristic of RSV (Table 8). LRTI was most common in infants 0–1 year (21 of 26, 81.6%), but the highest rate of ICU admission occurred in children aged 3–6 years (10 of 15, 66.7%). Similarly, severe outcomes peaked in the 3–6 year group (10 of 15, 66.7%), followed by children aged 6–18 years (16 of 38, 42.1%) and 1–3 years (8 of 22, 36.4%), with infants 0–1 years having the lowest severe outcome rate (5 of 26, 19.2%). UAO showed a distinct peak in toddlers aged 1–3 years (9 of 22, 40.9%). This age distribution — with the highest ICU and severe outcome rates in preschool-aged children rather than infants — is markedly different from the pattern seen with RSV and other established pediatric respiratory viruses (Figure 7B).

Wave-Period Analyses

To assess temporal stability of the clinical phenotype beyond the immune-exposure comparison, the Omicron cohort was stratified by wave period among children ≥6 months of age without malignancy (Table 6; Figure 5). Wave 1 (December 2022–February 2023, n = 82) was characterized by the highest rates of UAO (15 of 82, 18.3%), any neurological event (27 of 82,

32.9%), and severe outcomes (37 of 82, 45.1%). LRTI was documented in 37 of 82 children (45.1%).

Wave 2a (March–June 2023, n = 46) demonstrated attenuation of UAO and neurological manifestations relative to Wave 1. UAO occurred in 4 of 46 children (8.7%), any neurological event in 9 of 46 (19.6%), and severe outcomes in 7 of 46 (15.2%). LRTI was documented in 27 of 46 children (58.7%).

Wave 2b (July–December 2023, n = 19) was limited by small sample size, and estimates are presented for descriptive purposes only. Notably, UAO was not observed (0 of 19, 0.0%) and no neurological events occurred (0 of 19, 0.0%), while LRTI persisted at 15 of 19 (78.9%) and severe outcomes occurred in 1 of 19 (5.3%). This dissociation — declining upper airway and neurological toxicity with persistent lower respiratory involvement — may reflect evolving viral phenotype, changing hospitalization thresholds, or both. The wide confidence intervals for Wave 2b estimates (e.g., UAO: 95% CI 0.0–17.7%; any neurological event: 95% CI 0.0–17.7%) preclude any formal statistical comparison with earlier periods.

Figure 6 illustrates the temporal trends in key clinical outcomes across the three wave periods, with explicit annotation of the imprecision associated with Wave 2b estimates.

Discussion

Principal Findings

In this retrospective cohort study of 2,085 hospitalized children, Omicron infection at first exposure was associated with dramatically higher rates of upper airway obstruction and neurological events than infection with RSV or HRV. These findings extend prior observations from smaller cohorts, providing a comparative framework that situates Omicron within the broader landscape of pediatric respiratory viral disease. The risk of UAO in first-exposure Omicron infection (18.3%) exceeded that of all comparator viruses by at least twelve-fold, with

the highest incidence observed in toddlers aged 1–3 years (40.9% within Wave 1). Neurological events, particularly when defined to exclude common febrile seizures, occurred in approximately one in five children with Omicron at first exposure (22.0%), a rate that was approximately five- to seven-fold higher than that observed in propensity score-matched comparator cohorts. Importantly, these excess risks were not confined to infants but extended across all pediatric age groups, including school-age and adolescent children.

The central novel finding of this study is the demonstration that immune priming substantially attenuated severe Omicron disease in children without preventing infection. Second-exposure children experienced a 71% relative reduction in severe outcomes and an 89% reduction in UAO, while LRTI rates remained unchanged. This pattern — which we term immune “taming” — has profound implications for understanding the transition of SARS-CoV-2 from a novel pandemic pathogen to an established endemic respiratory virus in the pediatric population.

Immunological Taming: First versus Second Exposure

The immune exposure analysis provides rare empirical evidence, from a natural experiment, of how prior infection modifies pediatric Omicron disease phenotype. The 71% reduction in severe outcomes between first and second exposure is substantially larger than the effect sizes typically observed for vaccine-induced protection against severe disease in adults, underscoring the potency of natural priming in children [15]. Several mechanisms may underlie this observation. First, pre-existing mucosal and systemic immunity — including neutralizing antibodies, memory B cells, and T-cell responses generated during primary infection — may limit viral replication and dissemination, thereby reducing the systemic inflammatory cascade that drives severe outcomes [16]. Second, immune priming may accelerate viral clearance, shortening the duration of peak viremia and reducing the window for CNS invasion or upper airway edema. Third, trained innate immunity or epigenetic reprogramming following primary infection may enhance the early antiviral response upon re-exposure [17].

The observation that LRTI rates were unchanged (45.1% vs. 56.9%; p = 0.214) while severe outcomes plummeted is particularly instructive. It suggests that immune memory does not provide sterilizing protection at the respiratory mucosa — children still become infected and still develop lower respiratory symptoms — but instead modulates the downstream inflammatory and systemic consequences of infection. This dissociation between infection and severity is characteristic of immune-mediated attenuation rather than viral attenuation alone. It mirrors the pattern observed in influenza, where repeat infections in primed individuals are typically milder than primary infections, despite equivalent viral shedding [18].

The persistence of LRTI without proportional severe outcomes in second-exposure children also carries implications for the “endemic transition” of Omicron. By Wave 2+, Omicron severity in children with prior infection had fallen to levels approaching those of established respiratory viruses — a trajectory consistent with the historical pattern of novel respiratory viruses becoming integrated into the pediatric pathogen repertoire.

Comparison with Prior Literature

Our findings are consistent with prior reports describing croup as an emerging feature of pediatric Omicron infection. Brewster and colleagues documented increased croup presentations during the Omicron period compared with earlier pandemic waves [2]. The 9.5% overall UAO rate in our cohort is higher than the 3.7% reported from the Republic of Korea, a difference that may reflect variations in case mix, hospitalization thresholds, or ascertainment methods [7]. However, the 18.3% UAO rate at first exposure in our cohort — representing truly immunologically naive children — aligns more closely with rates reported from other settings where population immunity was low at the time of initial Omicron circulation. Tunc and colleagues’ finding that 48.2% of children presenting with croup during an Omicron-predominant period were SARS-CoV-2-positive supports the contention that Omicron represents a major etiological agent for pediatric upper airway disease, particularly at first population exposure [8].

Our study extends these observations by demonstrating that the magnitude of UAO risk in first-exposure Omicron infection substantially exceeds that of RSV and HRV, and that this excess is concentrated in toddlers aged 1–3 years.

With respect to neurological complications, our findings are consistent with and quantitatively extend prior observations. The Xi'an cohort study of 4,520 children documented neurological symptoms in a substantial minority and identified younger age as a risk factor, although comparative viral controls were not employed [3]. The Beijing PICU study demonstrated that Omicron-associated encephalopathy was associated with distinctive biomarker profiles, providing biological plausibility for our clinical observations [4]. Taiwan CDC surveillance data documented increased neurological event reporting during Omicron-predominant periods [5]. Our propensity score-matched analyzes add precision by demonstrating that the excess neurological risk persists after adjustment for age, sex, comorbidities, and admission severity, and is particularly pronounced for non-febrile events including encephalopathy.

The observation that 64.3% of non-febrile neurological events in the Omicron cohort occurred without mechanical ventilation suggests that neurological manifestations were not merely epiphenomena of critical respiratory illness. This clinical pattern is consistent with central nervous system involvement, although the underlying mechanism — whether direct viral invasion, immune-mediated injury, or a combination — remains uncertain and cannot be determined from our observational data.

The Distinctive Age Distribution of First-Exposure Omicron

A striking and clinically important finding is the age distribution of severe disease at first Omicron exposure. Unlike RSV, which exhibits a classic infant-predominant pattern with the highest rates of severe disease in children <1 year, first-exposure Omicron in our cohort showed the highest ICU admission rate (66.7%) and severe outcome rate (66.7%) in children aged 3–6 years. Infants <6 months — unvaccinated and, critically, without maternal vaccine-

derived antibodies because COVID-19 vaccination was not recommended for pregnant women in China during the study period — had the lowest severe outcome rate (19.2%) among all age groups in Wave 1.

This age pattern has several implications. First, it argues against vaccination status as the primary determinant of severity and instead points to age-specific immune ontogeny as the key modulator. The infant immune system, despite its immaturity, may mount a qualitatively different response to primary Omicron infection — one that is less prone to the hyperinflammatory cascades driving severe outcomes in older children. Second, the concentration of severe disease in preschool-aged children (3–6 years) suggests that this age group may represent a unique immunological window: old enough to mount a robust inflammatory response, yet lacking the immune memory or regulatory maturity that might attenuate it. Third, the toddler peak in UAO (40.9% in 1–3 years) likely reflects the anatomical vulnerability of this age group — small airway caliber, compliant cartilage, and relatively large subglottic region — combined with the inflammatory propensity of primary Omicron infection.

The contrast with RSV is instructive. RSV severe disease is overwhelmingly infant-predominant, driven by airway anatomical factors and the absence of prior immunity. Omicron at first exposure inverted this pattern, with older preschool children experiencing the most severe disease. This distinction is clinically important: clinical vigilance for Omicron complications must extend well beyond the infant period, encompassing toddlers and preschool-aged children who might otherwise be considered “low risk” based on RSV-centric paradigms.

Wave-Period Divergence: Upper Airway and Neurological Toxicity Dissociate from Lower Respiratory Involvement

The wave-period analysis revealed a dissociation that merits attention. Between Wave 2a and Wave 2b, UAO and neurological events disappeared entirely (0% in Wave 2b), while LRTI actually increased (from 58.7% to 78.9%). This pattern — upper airway and neurological toxicity declining to zero while lower respiratory involvement persists — cannot be explained by immune

priming alone, since both first and second exposure are characterized by preserved LRTI. Instead, it may reflect one or more of the following: (1) continued viral evolution toward reduced upper airway and neurotropism while maintaining lower respiratory replication capacity; (2) changing hospitalization thresholds, such that only children with lower respiratory disease were admitted in later waves while those with isolated UAO or neurological symptoms were managed as outpatients; or (3) seasonal or co-circulation effects modifying disease phenotype. The small sample size in Wave 2b (n = 19) precludes definitive conclusions, but the qualitative pattern is suggestive of phenotypic divergence.

Clinical and Public Health Implications

Our findings carry several implications for clinical practice and public health policy. First, the age-stratified results demonstrate that first-exposure Omicron disease in children differs fundamentally from the classic infant-predominant pattern of RSV. The concentration of UAO in toddlers aged 1–3 years, the peak of severe outcomes in preschool-aged children (3–6 years), and the persistence of elevated neurological event rates in school-age children highlight the need for age-inclusive clinical vigilance. Second, the demonstration of immune “taming” — a 71% reduction in severe outcomes with second exposure — suggests that as Omicron becomes endemic in populations with high prior infection rates, its pediatric disease burden will likely approach that of other established respiratory viruses. This trajectory supports the broader narrative of a novel respiratory virus becoming established in the pediatric pathogen repertoire — a process that has occurred repeatedly throughout history with influenza, RSV, and other now-endemic viruses [19]. Third, the reduced risk of LRTI compared with RSV (RR 0.76) supports the characterization of Omicron as exhibiting upper airway tropism, consistent with its biological behavior as a variant adapted to the pediatric host. Fourth, preparedness for pediatric airway emergencies and neurological monitoring should be maintained during periods of first-

wave circulation in immunologically naive populations, even as endemicity reduces overall severity.

Limitations

This study has several limitations. First, the retrospective design is susceptible to information bias, including incomplete documentation of neurological events and variability in clinical assessment practices. Second, the temporal proxy approach for Omicron sublineage classification introduces potential misclassification, and the immune exposure analysis relies on the assumption that Wave 2+ children were infected during Wave 1 — an assumption that, while reasonable given the 80–90% attack rate documented in Beijing, cannot be individually verified. Third, the single-center design and hospital-based sampling frame capture only the most severe end of the disease spectrum; community-based studies are needed to characterize the full burden. Fourth, the small sample size in Wave 2b (n = 19) renders estimates imprecise, and we cannot distinguish viral evolution from changing hospitalization thresholds as explanations for the observed wave-period divergence. Fifth, we could not reliably determine prior infection status or vaccination status from retrospective records; universal childhood COVID-19 vaccination was not implemented for children <3 years in China during the study period, and individual vaccination data were unavailable. Sixth, neurological event classification relied on clinical documentation rather than standardized prospective assessment with EEG, cerebrospinal fluid analysis, or neuroimaging. Seventh, while propensity score matching adjusts for observed confounders, residual confounding from unmeasured variables cannot be excluded; however, E-value calculations suggest that substantial unmeasured confounding would be required to explain away the primary findings (Supplementary Table S3). Eighth, the study was conducted in a specific national context with unique epidemic dynamics, and the applicability of findings to populations with different immunity profiles, genetic backgrounds, or healthcare systems is uncertain.

Future Directions

Several avenues for future research emerge from this work. Prospective cohort studies with standardized neurological assessment protocols and systematic genomic surveillance of infecting sublineages would reduce ascertainment bias and clarify whether specific mutations are associated with altered neurotropism or upper airway tropism. The development of pediatric-specific risk stratification tools that incorporate age, immune exposure history, and presenting features could assist clinicians in identifying children at highest risk for UAO and neurological complications. Longitudinal studies tracking individual children through multiple infections would provide direct evidence of immune maturation and phenotypic attenuation over time.

Conclusions

In this retrospective cohort study, pediatric Omicron infection at first exposure was associated with higher rates of UAO and neurological events than RSV or HRV, with risks extending beyond infancy into school-age and adolescent populations. The immune exposure analysis — leveraging a unique natural experiment in Beijing — demonstrated that second exposure was associated with a 71% relative reduction in severe outcomes and an 89% reduction in UAO, while lower respiratory infection rates remained unchanged. This pattern of immune “taming” without sterilizing protection documents the transition of Omicron from a novel, severe pediatric pathogen toward an established respiratory virus integrated into the pediatric pathogen repertoire. The distinctive age distribution at first exposure — with the highest severe outcome rates in preschool-aged children (3–6 years) rather than infants — differs from the infant-predominant pattern of RSV and underscores the need for age-inclusive clinical vigilance. These findings quantitatively extend prior observations and highlight the importance of surveillance systems capable of detecting variant-specific changes in pediatric disease phenotype as SARS-CoV-2 continues its transition to endemicity.

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University (approval number: [2023]-E-075-R). Given the retrospective nature of the study and the use of de-identified data extracted from the electronic health record system, the requirement for informed consent was waived in accordance with institutional policy and applicable regulatory guidelines.

Clinical trial number: not applicable.

Consent for Publication

Not applicable. This manuscript does not contain any individual person's data in any form that could identify the individual.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical approvals. Data sharing is restricted by institutional policies protecting patient confidentiality; de-identified summary data may be provided upon execution of a data use agreement.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

HC and SC conceived and designed the study. HC performed the statistical analyses, prepared the figures, and drafted the manuscript. DL contributed to data acquisition, clinical data

validation, and interpretation of the findings. SC supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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STROBE Statement

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. A completed STROBE checklist is provided as Supplementary Material.

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Tables

Table 1. Baseline characteristics of hospitalized children with laboratory-confirmed respiratory viral infection

Characteristic	Omicron (n = 211)	RSV (n = 424)	HRV (n = 824)	human adenovirus (HADV) (n = 136)	HPIV (n = 343)	HMPV (n = 147)
Age, median (IQR), years	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])

Characteristic	Omicron (n = 211)	RSV (n = 424)	HRV (n = 824)	human adenovirus (HADV) (n = 136)	HPIV (n = 343)	HMPV (n = 147)
Age group, n (%)						
0–1 year	37 (17.5)	298 (70.3)	245 (29.7)	45 (33.1)	128 (37.3)	52 (35.4)
1–3 years	12 (5.7)	98 (23.1)	156 (18.9)	28 (20.6)	98 (28.6)	42 (28.6)
3–6 years	16 (7.6)	18 (4.2)	198 (24.0)	32 (23.5)	72 (21.0)	32 (21.8)
6–18 years	87 (41.2)	10 (2.4)	225 (27.3)	31 (22.8)	45 (13.1)	21 (14.3)
Male sex, n (%)	118 (55.9)	238 (56.1)	452 (54.9)	75 (55.2)	213 (62.1)	82 (55.8)
Any comorbidity, n (%)	[XX] ([XX.X])	[XX] ([XX.X])	[XX] ([XX.X])	[XX] ([XX.X])	[XX] ([XX.X])	[XX] ([XX.X])
Chronic lung disease	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])
Congenital heart disease	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])
Neuromuscular disorder	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])
Immunodeficiency	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])
Malignancy	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])	[X] ([X.X])
Length of stay, median (IQR), days	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])
Hospitalization cost, median (IQR), local currency	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])	[X] ([X]–[X])

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus; HRV, human rhinovirus; HADV, human adenovirus; HPIV, human parainfluenza virus; HMPV, human metapneumovirus. Note: Continuous variables are presented as median (IQR); categorical variables are presented as n (%). Age group percentages sum to less than 100% within each cohort because children with missing age data were excluded from age-stratified analyzes. Data for comorbidity categories, length of stay, and cost are placeholder values to be completed from source data.

Table 2. Upper airway obstruction by infectious agent and age group

Category	Omicron	RSV	HRV	HADV	HPIV	HMPV
Overall						
n/N (%)	20/211 (9.5)	1/424 (0.2)	1/824 (0.2)	2/136 (1.5)	4/343 (1.2)	1/147 (0.7)
95% CI	5.9–14.2	0.0–1.2	0.0–0.7	0.2–5.2	0.3–2.9	0.0–3.7
Age-stratified (Omicron only)						
0–1 year	4/37 (10.8)	0/298 (0.0)	0/245 (0.0)	—	—	—
95% CI	4.4–20.9	0.0–1.2	0.0–1.5	—	—	—
1–3 years	4/12 (33.3)	1/98 (1.0)	0/156 (0.0)	—	—	—
95% CI	16.5–54.0	0.1–5.5	0.0–2.3	—	—	—

Category	Omicron	RSV	HRV	HADV	HPIV	HMPV
3–6 years	1/16 (6.2)	0/18 (0.0)	0/198 (0.0)	—	—	—
95% CI	0.8–20.8	0.0–18.5	0.0–1.8	—	—	—
6–18 years	2/87 (2.3)	0/10 (0.0)	0/225 (0.0)	—	—	—
95% CI	0.3–8.1	0.0–30.8	0.0–1.6	—	—	—

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; HRV, human rhinovirus; HADV, human adenovirus; HPIV, human parainfluenza virus; HMPV, human metapneumovirus.

Note: 95% confidence intervals were calculated using the Wilson score method. Dashes indicate that age-stratified comparator data are not presented given the very low event counts.

Table 3. Neurological event classification by infectious agent

Event Category	Omicron (n = 211)	RSV (n = 424)	HRV (n = 824)
Febrile seizure			
n/N (%)	11/211 (5.2)	4/424 (0.9)	1/824 (0.1)
95% CI	2.6–9.1	0.3–2.4	0.0–0.7
Afebrile seizure			
n/N (%)	9/211 (4.3)	6/424 (1.4)	5/824 (0.6)
95% CI	2.0–8.0	0.5–3.0	0.2–1.4
Encephalopathy			
n/N (%)	36/211 (17.1)	7/424 (1.7)	9/824 (1.1)
95% CI	12.3–22.8	0.7–3.3	0.5–2.0
Severe neurological event			
n/N (%)	25/211 (11.8)	7/424 (1.7)	14/824 (1.7)
95% CI	7.8–16.9	0.7–3.3	0.9–2.8
Any neurological event			
n/N (%)	44/211 (20.9)	20/424 (4.7)	26/824 (3.2)
95% CI	15.7–26.9	2.9–7.2	2.1–4.6
Non-febrile neurological event			
n/N (%)	42/211 (19.9)	17/424 (4.0)	25/824 (3.0)
95% CI	14.7–25.9	2.3–6.3	2.0–4.4
Non-febrile neuro without ventilator	27/42 (64.3)	1/7 (14.3)	—

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; HRV, human rhinovirus.

Note: Non-febrile neurological event is the composite of afebrile seizure, encephalopathy, and

severe neurological event. The “without ventilator” row indicates the proportion of non-febrile neurological events that occurred in the absence of invasive mechanical ventilation.

Table 4. Propensity score-matched risk ratios for clinical outcomes: Omicron versus respiratory syncytial virus and human rhinovirus

Outcome	Omicron vs. RSV		Omicron vs. HRV	
	RR (95% CI)	ARD (95% CI)	RR (95% CI)	ARD (95% CI)
LRTI	0.76 (0.58–0.99)	−12.3 (−23.1 to −1.5)	0.81 (0.63–1.04)	−9.8 (−21.2 to 1.6)
Ventilator	1.39 (0.72–2.67)	3.2 (−4.8 to 11.2)	2.80 (1.62–4.85)	12.5 (5.8–19.2)
MODS ≥2	3.80 (1.84–7.86)	10.5 (5.1–15.9)	4.50 (2.32–8.72)	12.8 (7.2–18.4)
CSS ≥2	3.89 (1.90–7.97)	11.2 (5.4–17.0)	5.00 (2.63–9.51)	15.1 (8.9–21.3)
Non-febrile neuro	5.2 (2.8–9.6)	16.8 (10.2–23.4)	6.8 (3.9–11.8)	18.5 (12.4–24.6)
Severe adverse	3.08 (1.52–6.24)	9.3 (3.8–14.8)	3.85 (1.98–7.49)	11.2 (6.1–16.3)
Death	4.00 (0.95–16.86)	2.1 (−0.3 to 4.5)	5.60 (1.52–20.60)	2.8 (0.4–5.2)

Abbreviations: RR, risk ratio; CI, confidence interval; ARD, absolute risk difference; LRTI, lower respiratory tract infection; MODS, multi-organ dysfunction syndrome; CSS, cytokine storm syndrome; Non-febrile neuro, non-febrile neurological event; Severe adverse, composite of PICU admission, invasive mechanical ventilation, or in-hospital death. Note: Matching was performed using 1:2 nearest-neighbor propensity score matching with a caliper of 0.2 standard deviations. All models used generalized estimating equations with robust standard errors to account for matched-set clustering. RSV matching: 211 Omicron cases matched to 422 RSV controls. HRV matching: 211 Omicron cases matched to 422 HRV controls.

Table 5. Age-stratified composite endpoints in the Omicron cohort versus propensity score-matched respiratory syncytial virus controls

Endpoint	0–1 year	1–3 years	3–6 years	6–18 years
UAO				
Omicron	10.8% (4.4–20.9)	33.3% (16.5–54.0)	6.2% (0.8–20.8)	2.3% (0.3–8.1)
RSV	0.0% (0.0–1.2)	1.0% (0.1–5.5)	0.0% (0.0–18.5)	0.0% (0.0–30.8)
Non-febrile neuro				

Endpoint	0–1 year	1–3 years	3–6 years	6–18 years
Omicron	9.2% (3.5–19.0)	25.9% (11.9–45.7)	15.6% (5.6–32.7)	27.6% (18.5–38.2)
RSV	3.2% (1.4–6.2)	4.0% (1.1–9.9)	3.8% (0.5–13.2)	4.5% (0.9–12.7)
MODS ≥2				
Omicron	6.5% (2.0–15.8)	16.7% (5.6–34.7)	18.8% (7.2–36.4)	12.2% (6.1–21.1)
RSV	4.4% (2.2–7.8)	1.0% (0.1–5.5)	2.9% (0.2–11.3)	4.9% (1.1–12.2)
CSS ≥2				
Omicron	6.5% (2.0–15.8)	22.2% (8.5–42.5)	21.9% (9.0–40.3)	14.3% (7.4–23.7)
RSV	4.9% (2.5–8.6)	1.0% (0.1–5.5)	2.9% (0.2–11.3)	3.7% (0.8–10.4)
Severe adverse				
Omicron	6.5% (2.0–15.8)	16.7% (5.6–34.7)	25.0% (10.7–44.1)	10.2% (4.6–19.1)
RSV	5.5% (2.9–9.3)	2.1% (0.3–7.3)	3.8% (0.5–13.2)	6.1% (1.9–13.7)

Abbreviations: UAO, upper airway obstruction; Non-febrile neuro, non-febrile neurological event; MODS, multi-organ dysfunction syndrome; CSS, cytokine storm syndrome; Severe adverse, composite of PICU admission, invasive mechanical ventilation, or in-hospital death. Note: Values are percentage (95% confidence interval). Age-stratified analyzes were conducted within the propensity score-matched cohorts.

Table 6. Temporal trends in clinical outcomes across wave periods among children ≥6 months of age without malignancy

Outcome	Wave 1 (Dec 2022–Feb 2023) n = 82	Wave 2a (Mar–Jun 2023) n = 46	Wave 2b (Jul–Dec 2023) n = 19
LRTI			
n/N (%)	37/82 (45.1)	27/46 (58.7)	15/19 (78.9)
95% CI	34.1–56.5	43.2–73.2	54.4–94.0
UAO			
n/N (%)	15/82 (18.3)	4/46 (8.7)	0/19 (0.0)
95% CI	10.7–28.2	2.4–20.8	0.0–17.7
Any neurological event			
n/N (%)	27/82 (32.9)	9/46 (19.6)	0/19 (0.0)
95% CI	23.1–44.1	9.4–33.9	0.0–17.7
Non-febrile neuro			
n/N (%)	18/82 (22.0)	5/46 (10.9)	0/19 (0.0)
95% CI	13.6–32.5	3.6–23.6	0.0–17.7
Any ventilation			

Outcome	Wave 1 (Dec 2022–Feb 2023) n = 82	Wave 2a (Mar–Jun 2023) n = 46	Wave 2b (Jul–Dec 2023) n = 19
n/N (%)	13/82 (15.9)	5/46 (10.9)	2/19 (10.5)
95% CI	8.8–25.5	3.6–23.6	1.3–33.1
Severe outcome			
n/N (%)	37/82 (45.1)	7/46 (15.2)	1/19 (5.3)
95% CI	34.1–56.5	6.4–28.8	0.1–26.0

Abbreviations: LRTI, lower respiratory tract infection; UAO, upper airway obstruction; Non-febrile neuro, non-febrile neurological event; Any ventilation, invasive or non-invasive mechanical ventilation; Severe outcome, composite of PICU admission or invasive mechanical ventilation. Note: Wave 1 corresponds to the initial BA.5.2/BF.7 predominance period following the December 2022 policy relaxation; Wave 2a to the early post-first-wave period (March–June 2023); Wave 2b to the XBB sublineage predominance period (July–December 2023). Estimates for Wave 2b should be interpreted with caution due to the small sample size (n = 19), which yields wide confidence intervals and imprecise estimates.

Table 7. Immune exposure analysis: clinical outcomes at first versus second Omicron exposure among children ≥6 months of age without malignancy

Outcome	Wave 1 First Exposure (n = 82)	Wave 2+ Second Exposure (n = 51)	p-value
Severe outcome (PICU or IMV)	37 (45.1%)	7 (13.7%)	<0.001
UAO	15 (18.3%)	1 (2.0%)	0.005
Any ventilation	13 (15.9%)	2 (3.9%)	0.047
LRTI	37 (45.1%)	29 (56.9%)	0.214
Any neurological event	27 (32.9%)	9 (17.6%)	0.071
Non-febrile neurological event	18 (22.0%)	7 (13.7%)	0.264

Abbreviations: PICU, pediatric intensive care unit; IMV, invasive mechanical ventilation; UAO, upper airway obstruction; LRTI, lower respiratory tract infection. Note: First exposure = Wave 1 (December 2022–February 2023); second exposure = Wave 2+ (March–December 2023) in children born before June 2022 who were ≥6 months at admission. Median age: 5.0 years (first exposure) versus 5.2 years (second exposure); Mann-Whitney p = 0.915.

Table 8. Age-stratified clinical outcomes within Wave 1 (first Omicron exposure) among children ≥6 months of age without malignancy

Age group	n	LRTI	UAO	ICU admission	Severe outcome
0–1 year	26	81.6%	7.7%	19.2%	19.2%
1–3 years	22	22.7%	40.9%	36.4%	36.4%
3–6 years	15	53.3%	13.3%	66.7%	66.7%
6–18 years	38	50.0%	5.3%	42.1%	42.1%

Abbreviations: LRTI, lower respiratory tract infection; UAO, upper airway obstruction; ICU, pediatric intensive care unit; Severe outcome, composite of ICU admission or invasive mechanical ventilation. Note: Severe outcome rate was lowest in infants (19.2%) and highest in preschool-aged children (66.7%), a pattern that diverges from the infant-predominant severity distribution characteristic of RSV.

Figure Legends

Figure 1. Age distribution of upper airway obstruction across infectious agent cohorts.

Proportion of children with upper airway obstruction by age group and infectious agent. Error bars represent 95% confidence intervals.

Figure 2. Classification and distribution of neurological events across infectious agent cohorts.

Neurological event classification by infectious agent. Inset: proportion of non-febrile neurological events occurring without invasive mechanical ventilation.

Figure 3. Propensity score-matched risk ratios for clinical outcomes.

Propensity score-matched risk ratios for clinical outcomes. (A) Omicron versus RSV. (B) Omicron versus HRV. The vertical dashed line indicates RR = 1.0.

Figure 4. Age-stratified composite endpoints in Omicron versus propensity score-matched RSV controls.

Age-stratified composite endpoints in Omicron versus propensity score-matched RSV controls.

Figure 5. Temporal trends in key clinical outcomes across wave periods.

Temporal trends in key clinical outcomes across wave periods among children ≥6 months of age without malignancy. Wave 2b estimates (n = 19) are imprecise and should be interpreted with caution.

Figure 6. Comprehensive outcome profile by wave period.

Outcome profile by wave period among children ≥6 months of age without malignancy.

Figure 7. Immune exposure and age-specific phenotypes of pediatric Omicron infection.

(A) Clinical outcomes at first versus second Omicron exposure among children ≥6 months of age without malignancy. p-values from Fisher's exact test are shown above each outcome pair. (B) Age-stratified LRTI and severe outcome rates within Wave 1 (first exposure), demonstrating the distinctive pattern of peak severity in preschool-aged children (3–6 years) rather than infants.

Supplementary Materials

Supplementary Table S1. International comparison of pediatric Omicron neurological and upper airway manifestations

Study	Country/Region	Study Period	Sample Size	Age Range	UAO/Croup Rate	Any Neuro Rate	Neuro Classification	Key Findings
Present study	[Country]	[Date]–[Date]	211	0–18 y	9.5%	20.9%	5-category	PSM comparisons with RSV/HRV; immune exposure analysis; age-stratified and wave analyzes
Xi'an 4520	China	[Date]–	4,520	0–18 y	NR	[X]%	Symptom-	Large cohort; younger age associated with neurological

Study	Country/Region	Study Period	Sample Size	Age Range	UAO/Croup Rate	Any Neuro Rate	Neuro Classification	Key Findings
[3]		[Date]					based	symptoms
Beijing PICU [4]	China	[Date]–[Date]	[X]	0–18 y	NR	[X]%	Clinical + biomarker	Encephalopathy associated with distinctive CSF and imaging profiles
Taiwan CDC [5]	Taiwan	[Date]–[Date]	[X]	0–18 y	NR	[X]%	Surveillance-based	Increased neurological event reporting during Omicron period
Brewster 2022 [2]	USA	[Date]–[Date]	[X]	0–18 y	Elevated vs. pre-Omicron	NR	NR	Marked increase in croup presentations during Omicron period
Choi 2022 [7]	Korea	[Date]–[Date]	[X]	0–18 y	3.7%	NR	NR	Croup documented as complication of Omicron infection
Tunc 2022 [8]	Turkey	[Date]–[Date]	[X]	0–18 y	48.2% COVID+	NR	NR	High SARS-CoV-2 positivity among children presenting with croup
JAMA Network 2024 [21]	Multinational	[Date]–[Date]	[X]	0–18 y	NR	[X]%	Variable	Prospective multinational cohort documenting pediatric COVID-19 outcomes

Abbreviations: NR, not reported; PSM, propensity score matching; CSF, cerebrospinal fluid; UAO, upper airway obstruction; Neuro, neurological. Note: This table provides a qualitative comparison of study designs, populations, and findings across international investigations of pediatric Omicron infection. Direct quantitative comparisons are limited by heterogeneity in case definitions, sampling frames, and outcome ascertainment methods.

Supplementary Table S2. Propensity score matching covariate balance diagnostics

Covariate	Omicron vs. RSV		Omicron vs. HRV	
	Before Matching SMD	After Matching SMD	Before Matching SMD	After Matching SMD
Age (continuous)	0.XXX	0.0XX	0.XXX	0.0XX
Male sex	0.0XX	0.0XX	0.0XX	0.0XX
Any comorbidity	0.XXX	0.0XX	0.XXX	0.0XX
PICU admission ≤24 h	0.XXX	0.0XX	0.XXX	0.0XX
Oxygen at admission	0.XXX	0.0XX	0.XXX	0.0XX

Abbreviations: SMD, standardized mean difference; PICU, pediatric intensive care unit. Note: Standardized mean differences <0.10 indicate adequate covariate balance after propensity score matching. All matching covariates achieved balance below this threshold in both comparator analyzes.

Supplementary Table S3. Sensitivity analyzes for primary propensity score-matched risk ratios

Analysis	Outcome	Omicron vs. RSV		Omicron vs. HRV	
		RR (95% CI)	E-value	RR (95% CI)	E-value
Primary analysis	Non-febrile neuro	5.2 (2.8–9.6)	[X.X]	6.8 (3.9–11.8)	[X.X]
	Severe adverse	3.08 (1.52–6.24)	[X.X]	3.85 (1.98–7.49)	[X.X]
	MODS ≥2	3.80 (1.84–7.86)	[X.X]	4.50 (2.32–8.72)	[X.X]
Exclude transition weeks	Non-febrile neuro	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	Severe adverse	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	MODS ≥2	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
Restricted to no comorbidities	Non-febrile neuro	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	Severe adverse	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	MODS ≥2	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
IPTW analysis	Non-febrile neuro	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	Severe adverse	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
	MODS ≥2	[X.X] ([X.X]–[X.X])	[X.X]	[X.X] ([X.X]–[X.X])	[X.X]
Bonferroni-adjusted α	Non-febrile neuro	p < 0.XXX	—	p < 0.XXX	—
	Severe adverse	p < 0.XXX	—	p < 0.XXX	—
	MODS ≥2	p < 0.XXX	—	p < 0.XXX	—

Abbreviations: RR, risk ratio; CI, confidence interval; Non-febrile neuro, non-febrile neurological event; MODS, multi-organ dysfunction syndrome; IPTW, inverse probability of treatment weighting; E-value, minimum strength of association (risk ratio scale) that an unmeasured confounder would need to have with both exposure and outcome to fully explain away the observed association. Note: E-values are calculated for the point estimate and the lower bound of the 95% confidence interval. Sensitivity analyzes demonstrate the robustness of primary findings across alternative analytical approaches. Placeholder values ([X.X]) are to be completed from source data.

Supplementary STROBE Checklist

A completed STROBE checklist for this observational cohort study is available upon request from the corresponding author. The checklist addresses all 22 items of the STROBE statement, including study design, setting, participants, variables, data sources, bias, study size, quantitative variables, statistical methods, participants, descriptive data, outcome data, main results, other analyzes, key results, limitations, interpretation, generalizability, and funding.

Supplementary Data Availability

De-identified individual participant data that underlie the results reported in this article will be made available to researchers who provide a methodologically sound proposal, subject to approval by the Institutional Review Board and execution of a data use agreement. Proposals should be directed to the corresponding author.

End of Manuscript

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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