Intrinsic severity of SARS-CoV-2 Omicron BA.2 in uninfected, unvaccinated children: a population-based, case-control study on hospital complications

Winnie W.Y. Tso, MBBS[1,2,*], Mike Y.W. Kwan, MBBS[3,*], Yu Liang Wang, BSc[1], Lok Kan Leung, MSocSc[1], Daniel Leung,[1], Gilbert T. Chua, MBBS[1], Patrick Ip, MBBS[1], Wilfred H.S. Wong, PhD[1], Sophelia H.S. Chan, MBBS[1], Jasper F.W. Chan, MD[4], Malik Peiris, DPhil[5], Yu Lung Lau, MD[1,+], Jaime S. Rosa Duque, MD[1,+]

* *denotes co-first authors who contributed equally*

\+ *denotes all corresponding authors who contributed equally*

[1]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China
[2]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, China
[3]Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong, China
[4]State Key Laboratory of Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, The University of Hong Kong, Hong Kong, China
[5]School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China

Corresponding authors:

Jaime S Rosa Duque, MD, PhD
E-mail: jsrduque@hku.hk
(852) 2255 4806

Yu Lung Lau, MBChB, MD(Hons)
E-mail: lauylung@hku.hk
(852) 2255 4481

Running Title: intrinsic severity of SARS-CoV-2 Omicron BA.2

Keywords: COVID-19; Omicron; neurological; respiratory; children
Abstract Word Count: 262
Manuscript Word Count: 2680
Tables: 2
Supplementary Tables: 3

Research in context

Evidence before this study

We aimed to identify all available evidence on the severity of Omicron in children compared to other SARS-CoV-2 variants, influenza and parainfluenza viruses. On 17 Mar 29, 2022, we searched PubMed with the query ((“B.1.1.529” OR “Omicron” OR “VOC-21NOV-01”) AND (“SARS-CoV-2” OR “COVID-19” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus disease 2019” OR “Delta”) OR “influenza” OR “parainfluenza”) AND (“severity” OR “hospitalisation” OR “hospitalization” OR “hospital” OR “emergency care” OR “fatality” OR “mortality” OR “lethality” OR “death” OR “intensive care” OR “ventilation” OR “oxygen” OR “neurological” OR “seizure” OR “convulsion” OR “encephalitis” OR “encephalopathy” OR “respiratory” OR “pulmonary” OR “laryngotracheobronchitis” or “croup” OR “pneumonia” OR “lung”), with no date or language restrictions. We further searched the medRxiv and SSRN preprint databases using combinations of the above search terms and included additional relevant literature from the reference lists of identified publications. This search identified a total of 20 peer-reviewed papers and preprints. A cohort study from the United States (US) identified reduced hospitalization risk for young children aged <9 years infected with Omicron compared to Delta infection. However, a British cohort study found similar hospital admission rates between Omicron BA.1 and Delta waves for young children. A study from South Africa suggested increased seizure rates in children infected with Omicron BA.1, which was not observed with previous strains of SARS-CoV-2 variants. A majority of laryngotracheobronchitis, or croup, was due to Omicron, which doubled in incidence during its wave in the US.

Added value of this study

To date, this is the largest uninfected and unvaccinated childhood population to study the intrinsic severity of Omicron BA.2 by quantifying severe outcomes, including fatalities, paediatric intensive care (PICU) admissions, mechanical ventilation and oxygen use, seizures, encephalitis/encephalopathy, croup and pneumonia of hospitalised cases as compared to other past SARS-CoV-2 variants, influenza and parainfluenza viruses.

Implications of all the available evidence

The intrinsic severity of Omicron BA.2 in children who had no past COVID-19 or vaccination is not mild, and in fact, they had higher odds of PICU admissions, mechanical ventilation and oxygen use. Omicron BA.2 is more neuropathogenic than previous SARS-CoV-2 variants, influenza and parainfluenza viruses, resulting in more seizures. It also targets the upper airways more than past variants and influenza.

Abstract

Background: There has been a rapid surge of SARS-CoV-2 Omicron hospitalisations globally. However, the intrinsic severity of Omicron BA.2 is unknown, which could be determined by studying Hong Kong (HK) children who were both uninfected and unvaccinated before the Omicron wave.

Methods: This population-based study retrieved data from the HK territory-wide CDARS database of hospitalisations in all public hospitals and compared severe outcomes of the Omicron BA.2-dominant fifth wave (5 to 28 February 2022, n=1147), prior SARS-CoV-2 variants (1 January 2020 to 1 November 2021, n=737), and influenza and parainfluenza (1 January 2015 to 31 December 2019, n=32212 and n=16423, respectively) in children 0-11 years old. Outcomes included fatalities, paediatric intensive care unit (PICU) admissions and neurological and respiratory complications.

Findings: Four deaths (0.35%) occurred during the Omicron wave, resulting in a higher in-hospital case fatality rate than other SARS-CoV-2 variants (0%), influenza (0.05%) and parainfluenza (0.04%). PICU admission was higher for Omicron than other SARS-CoV-2 variants (OR=18.50, 95% CI 2.42-140.70, p=0.005) and influenza (OR=2.32, 95% CI 1.48-3.64, p<0.001). The proportion with neurological complications was 14.91% (171 out of 1,147) for Omicron, which was higher than influenza and parainfluenza (OR=1.75 95% CI 1.48-2.08 and OR=2.06 95% CI 1.74-2.46, p<0.001 for both, respectively). Croup occurred for Omicron more than other SARS-CoV-2 variants (OR=11.47, 95% CI 2.77-47.46 p = 0.001) and influenza (OR= 2.08, 95% CI 1.58-2.74 p<0.001) but not parainfluenza.

Interpretation: The intrinsic severity of Omicron BA.2 is not mild as evident by the fatality and severe complications of the uninfected and unvaccinated children.

Funding: HK Research Grants Council Collaborative Research Fund C7149-20G.

Introduction

During the pre-vaccination era of Coronavirus disease 2019 (COVID-19), 469982 out of 12 million children and young people <18 years old (CYP) in the United Kingdom (UK) had been reported to be infected with SARS-CoV-2 in the first year of the pandemic, mostly by the wild type and Alpha variant, and the infection fatality rate (IFR) was 5 per 100000 (0.005%)[1]. Since then, other variants, such as Beta, Gamma and Delta also swept across the globe, leading to over 6 million total deaths to date, of which 0.4% were estimated to be in children[2-5]. For many of those who survived, their convalescent sera demonstrated antibody protection across variants, which, in combination with vaccination, can induce hybrid immunity against COVID-19[6,7]. By the time Omicron emerged in November 2021, symptoms appeared to be milder than previous variants, and paediatric deaths were rare, but these were observed in populations in which a majority was already protected from a high degree of immunity from past infection, vaccination or both[8]. Therefore, the intrinsic severity of Omicron in children remains unknown[9,10].

The setting in Hong Kong (HK) can provide the prototypical platform for understanding the intrinsic severity of Omicron in children 0-11 years old. Since the onset of the pandemic, the HK Government implemented stringent social distancing policies, including universal masking, contact tracing, intermittent business closures and territory-wide school suspensions. From January 2020 to March 2022, school attendance was reduced from around 400 days to just 300 days, and even during reopening, students were allowed to attend only half-day of face-to-face lessons[11-15]. These measures were associated with one of the lowest recorded numbers of COVID-19 for the past 2 years in HK relative to other geographical regions[16]. Sero-epidemiological studies showed an infection rate of approximately 1% of the population of HK as of 31 October 2021 (Peiris-personal communication). Furthermore, COVID-19 vaccines were only approved for HK children aged 5-11 years old in mid-January 2022, so these children were both uninfected and unvaccinated at the start of the Omicron wave in HK[17]. The highly contagious Omicron, predominantly of the BA.2 sublineage in HK, led to exponential increases of SARS-CoV-2 infections of more than 900000 new cases since the start of the fifth wave of COVID-19 between 31 December 2021 to 15 March 2022 as compared to the mere 14197 cases over a 2-year period throughout the first 4 waves[16,18].

Indeed, although children have generally experienced more favourable outcomes than older adults in HK during the first 4 waves as similarly observed internationally, recent studies have described disproportionately higher hospitalisation rates in children after the emergence of Omicron[19,20]. Furthermore, these cases appear to have a greater predilection for more severe complications affecting the neurological and respiratory systems. In an observational study of the first Omicron wave, likely predominated by the BA.1 sublineage, the most frequent clinical diagnoses linked to paediatric hospitalisation was seizure[8]. Other studies suggested that laryngotracheobronchitis, or croup, is more prevalent, severe and prolonged with Omicron than other variants[21-23]. Deaths in children infected with Omicron have occurred but were all related to complex underlying co-pathologies[8]. Such emerging data are reshaping the notion that Omicron may not be as mild as initially speculated.

To understand the intrinsic severity of Omicron, this population-based study aimed to describe Omicron BA.2-dominant fifth wave's severe outcomes in hospitalised children aged 0-11 years, who basically lack immune exposure to past COVID-19 infections or vaccination. Additionally, we compared the neurological and respiratory complications in hospitalised children aged 0-11 years during this fifth wave of COVID-19 to previous waves and to other common respiratory viruses—influenza and parainfluenza virus infections—before the COVID-19 pandemic.

Methods

Study design and patient groups

We conducted a population-based case-control observational study in HK by analysing electronic medical records retrieved from the Clinical Data Analysis and Reporting System (CDARS). CDARS is an HK territory-wide health registration system recording admissions of all 42 public hospitals under the HK Hospital Authority (HA). The database has been used for many high-quality population-based studies and has been shown to have highly accurate coding[24]. CDARS captures the majority of patient records, especially during the COVID-19 pandemic when almost all infected children were admitted to public hospitals for isolation and disease management during the first 4 waves[25].

Clinical data at the population level were retrieved from CDARS using ICD-9 diagnostic codes (Supplementary Table 1). Data on children (aged 0-11 years) hospitalised with COVID-19 infection during the Omicron-dominant fifth wave between 5 February and 28 February 2022 were extracted. Due to the rapid Omicron surge with potential delay in reporting of death cases into CDARS, we also counterchecked fatality data published by the Centre for Health Protection of the HK Government[26]. In addition, we extracted data on children who were hospitalised due to COVID-19 infection that predated the Omicron wave during the first 4 waves between 1 January 2020 and 1 November 2021. Data on children who were hospitalised with influenza and parainfluenza between 1 January 2015 and 31 December 2019 were also obtained.

The inputted ICD-9 coding was based on diagnosis of infections with the specific respiratory viruses by symptomatology and laboratory confirmation using the immunofluorescence assay and/or reverse transcription-polymerase chain reaction (RT-PCR) on their respiratory tract specimens. Similarly, children were diagnosed with COVID-19 using RT-PCR on their respiratory tract specimens. We excluded cases with co-infections of 2 or more respiratory viruses/SARS-CoV-2.

We extracted data on hospitalised children with COVID-19, influenza viruses or parainfluenza viruses, and categorized them according to the following outcomes:

A. Fatality and severe complications:
    1) Case fatality rate (CFR)
    2) Paediatric intensive care (PICU) admissions
    3) Mechanical ventilation
    4) Oxygen use
B. Neurological complications:
    1) Seizures
        i. Benign febrile seizures: non-focal seizures and fever on patients between 6 months to 5 years old, with no known history of epilepsy,
        ii. Seizure with fever: seizure association with fever on patients who are < 6 months and ≥6 years old, with no known history of epilepsy,

iii. Epilepsy with breakthrough seizures: Known history of epilepsy with recurrence of seizure during the febrile illness

2) Encephalitis/encephalopathy

C. Respiratory complications:

1) Croup
2) Pneumonia

To optimize the accuracy of the indication for PICU admission, only cases with diagnostic or procedural coding with intensive/critical care needs were counted. Additional data including child's demographic details were extracted for data analyses.

This study was approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HKW IRB UW 20-292) and the Kowloon West Cluster Research Ethics Committee Institutional Review Boards (KWC-REC KW/FR-20-086(148-10)).

Statistical analysis

Binary logistic regression was used to identify the odds ratio (OR) for the specified outcomes. Omicron cases were compared with other SAR-CoV-2 variants and other respiratory viral cases. For each logistic regression model, the complications or procedures were inputted as the criterion. For each comparison, a new variable was inputted as the predictor, with Omicron cases coded as "1" while cases with other SAR-CoV-2 variants and other respiratory viruses coded as "0." Sex and age were inputted as control variables. A critical alpha level of 0.016 was used after applying Bonferroni adjustment for comparison of multiple groups. SPSS 27.0 was used to perform the statistical analysis.

Role of funding source

The funder has no role in the study design, data collection, data analysis and interpretation or the writing of this manuscript.

Results

Hospitalisation due to COVID-19 and other respiratory viral infections

A total of 1147 children aged 0-11 years were hospitalized during the Omicron wave from 5 February to 28 February 2022 (Table 1). There were 920 (80.21%) aged 0-5 years (Supplementary Tables 2a & 2b). From 1 January 2020 to 1 November 2021 (other variants of first 4 COVID-19 waves), 737 (54.27% aged 0-5 years) were hospitalised due to COVID-19 infection. For all other respiratory viruses, 32212 children were hospitalised due to influenza infection (75.54% aged 0-5 years) and 16423 children due to parainfluenza infection (92.97% aged 0-5 years) between 1 January 2015 and 31 December 2019.

Case fatality rate due to COVID-19 and other respiratory viruses

Amongst the 1147 Omicron cases, 4 (0.35 %) COVID-19-associated deaths occurred. These included 11 months, 3 years, 4 years and 9 years old. Three of them had good past health. The 9-year-old child had Duchenne muscular dystrophy. All were not vaccinated against COVID-19. The cause of death for 2 cases was attributed to neurological causes: one with encephalopathy and the other with fulminant cerebral oedema, which recently became a recognized phenotype of encephalitis[27]. There was no COVID-19-associated death during the first 4 waves. The CFR of Omicron was higher than influenza (16 out of 32212, 0.05%; OR=7.07, [95%CI 2.34-21.33], p=0.001) and parainfluenza (7 out of 16423, 0.04%; OR=6.27, [95%CI (1.73-22.67), p=0.005) viral infections.

Severe complications and PICU admission due to COVID-19 and other respiratory viral infections

Twenty-one (1.83%) children with COVID-19 infection required PICU admission during the Omicron wave (Table 1). In contrast, only 1 (0.14%) child with COVID-19 required PICU admission during the first 4 waves. Two hundred and fifty-four (0.79%) children with influenza and 270 (1.64%) children with parainfluenza required PICU admission over the 5-year study period. The ORs of PICU admission during the Omicron-dominant wave were significantly higher than the first 4 waves by other SARS-CoV-2 variants (OR=18.50, [95% CI 2.42-140.70], p=0.005) and influenza (OR=2.32, [95% CI 1.48-3.64], p<0.001), but comparable to parainfluenza, after adjusting for age and gender (Table 2). Eight out of 1147 (0.70%) children infected with Omicron required mechanical ventilation compared to none of those infected with other SARS-CoV-2

variants. This rate was significantly higher than that of influenza (0.25%, OR=2.65, [95% CI 1.28-5.51], p=0.009) and similar to that of parainfluenza (0.65%). Eleven out of 1147 (0.96%) had oxygen use during the Omicron wave but there was none for those infected with other SARS-CoV-2 variants. This rate was again significantly higher than influenza (0.37%, OR=2.52, [95% CI 1.35-4.70], p=0.004) but not parainfluenza.

Neurological complications due to COVID-19 and other respiratory viruses

A total of 171 children with neurological complications were hospitalised during the Omicron-dominant wave (Table 1). The most common neurological complication was febrile seizure (11.60%), followed by seizure with fever (2.44%). Five (0.44%) children had COVID-associated encephalitis/encephalopathy. During the first 4 waves, there was no admission due to COVID-19-related seizures.

The odds of all seizure types in children infected with Omicron was higher than children with influenza (OR=1.72, [95% CI 1.45-2.04], p< 0.001) and parainfluenza (OR=2.01, [95% CI 1.69-2.40], p<0.001). No febrile seizure was recorded among children infected with other SARS-CoV-2 variants, and there were more febrile seizures among Omicron infected children aged 0-5 years old than those infected with influenza or parainfluenza viruses (Table Supplementary 3a). Children infected with Omicron had significantly increased risk of seizure with fever compared to those infected with influenza (OR=3.16, [95% CI 2.11-4.73], p<0.001) or parainfluenza (OR=4.83, [95% CI 2.90-8.09], p<0.001) viruses (Table 2). Children infected with Omicron had a significantly increased risk of encephalitis/encephalopathy compared to children with parainfluenza viruses (OR= 4.22, [95% CI 1.54-11.57], p=0.005), but not influenza viruses.

Respiratory complications due to COVID-19 and other respiratory viruses

A total of 61 out of 1147 (5.32%) of the children infected with Omicron developed croup. This rate was higher than other SARS-CoV-2 variants (2 out of 737, 0.27%, OR=11.47, [95% CI 2.77-47.46], p=0.001) and influenza (601 out of 32212, 1.87%, OR=2.08, [95% CI 1.58-2.74], p<0.001), but not parainfluenza (889 out of 16423, 5.41%, OR=1.06, [95% CI 0.81-1.39], p=0.678) viruses (Tables 1 and 2). The proportions of pneumonia during the Omicron-dominant wave were similar

to other SARS-CoV-2 variants but significantly lower than those infected with either influenza or parainfluenza viruses (Table 2).

Discussion

This population-based study provides solid evidence that Omicron BA.2 was highly transmissible, with 1147 children hospitalised in just 23 days during the rapidly rising phase of the Omicron wave, surpassing the 737 hospitalisations due to other SARS-CoV-2 variants in the previous 22 months. Omicron BA.2 appeared more pathogenic than previous SARS-CoV-2 variants and influenza virus in children, resulting in higher in-hospital CFR, more PICU admissions, mechanical ventilation and oxygen use. In addition, Omicron BA.2 appeared to be more neuropathogenic than previous SARS-CoV-2 variants, influenza and parainfluenza viruses in children, resulting in more seizures. However, the rates of encephalitis/encephalopathy were similar for Omicron BA.2 and influenza virus. Interestingly, Omicron BA.2 was more pathogenic in the upper airway relative to the lung as compared to previous SARS-CoV-2 variants and influenza virus in children, resulting in a higher percentage of croup. This observation is supported by evidence from *ex vivo* human lung cultures that Omicron replicates better in the bronchus than lung[28,29].

Our finding that Omicron BA.2 is associated with more severe hospital outcomes in children 0-11 years old appears to be in line with a recent age-specific analysis of hazard ratio (HR) of hospital admission with Omicron BA.1 compared with Delta in England[30]. This national cohort study found considerable variation in the severity of Omicron BA.1 relative to Delta cases with age. The adjusted HRs for hospital admission did not differ between these 2 variants for children <10 years old (HR 1.1), while this was greatly reduced for adults aged 20-69 years old (HR 0.25). This analysis was adjusted for multiple confounders, including previous infection status and vaccination, hence the intrinsic severity of Omicron could be assessed relative to that of Delta in different age groups. In a secondary analysis disaggregating further those younger than 10 years old, the relative risk was higher in those younger than 1 year of age than in those aged 1-4 years or 5-9 years. Again, this is in keeping with our observation the majority of deaths in our cohort were in children

<5 years old. We, however, caution our in-hospital CFR of 0.35% was an overestimate of fatality because many children with mild COVID-19 during the Omicron wave were not admitted but cared at home. Using the CHP database that reported approximately 13000 children 0-11 years old were infected between 5 and 28 February 2022, the IFR was estimated to be 0.02%, which was higher than that of 0.005% in the UK national study of CYP in the first year of pandemic[1,26].

Our observation that Omicron is associated with high percentages of seizures and croup in children is in line with previous clinical case series, emphasizing further the need for paediatricians to anticipate such complications, in particular, how to differentiate acute encephalitis from febrile seizure so as to reduce fatality and improve outcome[8,21-23].

In addition to being uninfected and unvaccinated previously, another possible explanation of why HK children under 5 years old infected with Omicron seem to have such unexpected severity could be due to the lack of exposure to seasonal human coronaviruses in the past 2 years, resulting in lack of cross-reactive immunity, in particular the more durable and broader T cell immunity[31-33].

This study had limitations. First, due to the rapid Omicron surge, there might be a time lag in reporting COVID-19 cases into the CDARS database. However, we have extensively cross-checked data on critical and death cases as reported by the HK Centre for Health Protection (CHP). Secondly, as genomic sequencing information is not encoded in CDARS, we cannot be certain that all COVID-19 cases during the fifth wave in our dataset were caused by Omicron BA.2. Nevertheless, based on publicly-available epidemiological data, even at the start of the Omicron surge in December, Omicron had become the dominant strain accounting for more than 60% of the total cases[34]. By March 2022, CHP reported that out of the 130 COVID-associated deaths with genome sequencing, 117 were Omicron and 13 were Delta[26]. The strengths of this study included the large sample size of the population-based study design, as well as comparison with hospital complications associated with influenza and parainfluenza, hence controlling confounders due to criteria of hospital admissions of children with seizures and croup. Pre-Omicron COVID-19 cases were all admitted only to public hospitals, not the private sector, and therefore CDARS would capture all hospitalized cases.

In conclusion, Omicron BA.2 can cause severe disease in unvaccinated children. Hence, vaccination should be rapidly implemented for children eligible, and in particular, for under 3 years old, extension of use of current vaccines should be urgently explored.

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Contributors

W Tso, JS Rosa Duque, MYW Kwan and YL Lau conceptualised the work. W Tso, JS Rosa Duque, YL Wang, LK Leung, SHS Chan and WHS Wong developed the methodology and curated the data. W Tso, YL Wang, LK Leung, JS Rosa Duque, MYW Kwan, GT Chua and P Ip handled project administration. W Tso, WHS Wong and P Ip acquired funding. W Tso, JS Rosa Duque, YL Wang, LK Leung and WHS Wong did the formal analysis. JS Rosa Duque, W Tso, MYW Kwan and YL Lau supervised the work. W Tso, JS Rosa Duque, YL Lau, M Peiris, JFW Chan, YL Wang, LK Leung, WHS Wong and D Leung validated the data. YL Wang, LK Leung and D Leung were responsible for visualization. W Tso, JS Rosa Duque, MYW Kwan and YL Lau wrote the original draft of the manuscript. All authors revised or reviewed the later versions and approved the final version of the manuscript.

Declaration of Interests

All authors declare no competing interests.

Data Sharing

All data used in this analysis were anonymised. Raw data can be obtained from JS Rosa Duque, and request for access to the underlying CDARS source information can be directed to HK Hospital Authority. Data from HK Centre for Health Protection were publicly available.

Funding

This study was supported by the Hong Kong Research Grants Council Collaborative Research Fund (C7149-20G).

Acknowledgments

We thank all health care personnel for caring for patients during the pandemic and administering vaccines to protect our community against COVID-19. We are particularly grateful to Dr Anita MC Tsang and Dr Janice CY Chow at the Department of Paediatric and Adolescent Medicine, Queen Mary Hospital, Hong Kong, China, for their suggestions on CDARS search. The funders played no direct role in the study. The views expressed are those of the authors and not necessarily those of the HK Government.

Table 1: **Clinical characteristics of all hospital admissions between the four respiratory infections.**

	SARS-CoV-2: Omicron BA.2 (n=1147)	SARS-CoV-2: Other Variants (n=737)	Influenza (n=32212)	Parainfluenza (n=16423)
Data period	05/02/2022 – 28/02/2022	01/01/2020 – 01/11/2021	01/01/2015 – 31/12/2019	01/01/2015 – 31/12/2019
Sex				
Male	661 (57.63%)	401 (54.41%)	17504 (54.34%)	9228 (56.19%)
Female	486 (42.37%)	336 (45.59%)	14708 (45.66%)	7159 (43.81%)
Age	3.38 (3.09)	5.71 (3.53)	4.14 (2.81)	2.62 (2.09)
0 to 5 years	920 (80.21%)	400 (54.27%)	24334 (75.54%)	15268 (92.97%)
6 to 11 years	227 (19.79%)	337 (45.73%)	7878 (24.46%)	1155 (7.03%)
Fatality and severe complications				
Case fatality rate	4 (0.35%)	0	16 (0.05%)	7 (0.04%)
PICU admissions	21 (1.83%)	1 (0.14%)	254 (0.79%)	270 (1.64%)

Mechanical ventilation	8 (0.70%)	0	82 (0.25%)	106 (0.65%)
Oxygen use	11 (0.96%)	0	120 (0.37%)	225 (1.37%)
Neurological complications	171 (14.91%)	0	2707 (8.40%)	1258 (7.66%)
All seizures	166 (14.47%)	0	2650 (8.23%)	1248 (7.60%)
Febrile seizures	133 (11.60%)	0	2303 (7.15%)	1142 (6.95%)
Seizures with fever	28 (2.44%)	0	290 (0.90%)	42 (0.26%)
Breakthrough seizures with epilepsy	5 (0.44%)	0	57 (0.18%)	64 (0.39%)
Encephalitis/encephalopathy	5 (0.44%)	0	78 (0.24%)	17 (0.10%)
Respiratory complications	70 (6.10%)	8 (1.09%)	2342 (7.27%)	2891 (17.60%)
Croup	61 (5.32%)	2 (0.27%)	601 (1.87%)	889 (5.41%)
Pneumonia	10 (0.87%)	6 (0.81%)	1756 (5.45%)	2030 (12.36%)
Croup/pneumonia ratio	6.10	0.33	0.34	0.44

Data are n (%), mean (SD) or median (IQR). PICU = paediatric intensive care units.

Table 2: **Odds ratios of neurological and respiratory complications and intensive care procedures in Omicron BA.2 cases in comparison to other viral infections**

	SARS-CoV-2 Omicron BA.2 vs SARS-CoV-2 Other Variants		SARS-CoV-2 Omicron BA.2 vs Influenza		SARS-CoV-2 Omicron BA.2 vs Parainfluenza	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Fatality and severe complications						
Case fatality rate	∞	NA	7.07 (2.34-21.33)	0.001*	6.27 (1.73-22.67)	0.005*
PICU admissions	18.50 (2.42-140.70)	0.005*	2.32 (1.48-3.64)	<0.001**	0.97 (0.62-1.53)	0.909
Mechanical ventilation	∞	NA	2.65 (1.28-5.51)	0.009*	0.96 (0.46-1.98)	0.905
Oxygen use	∞	NA	2.52 (1.35-4.70)	0.004*	0.68 (0.37-1.25)	0.214
Neurological complications	∞	NA	1.75 (1.48-2.08)	<0.001**	2.06 (1.74-2.46)	<0.001**
All seizures	∞	NA	1.72 (1.45-2.04)	<0.001**	2.01 (1.69-2.40)	<0.001**
Febrile seizures	∞	NA	1.42 (1.18-1.72)	<0.001**	1.79 (1.48-2.17)	<0.001**

Seizures with fever	∞	NA	3.16 (2.11-4.73)	<0.001**	4.83 (2.90-8.09)	<0.001**
Breakthrough seizures with epilepsy	∞	NA	2.66 (1.06-6.65)	0.037	0.92 (0.36-2.32)	0.857
Encephalitis/ encephalopathy	∞	NA	1.95 (0.79-4.83)	0.150	4.22 (1.54-11.57)	0.005*
Respiratory complications	4.21 (1.98-8.95)	<0.001**	0.81 (0.63-1.03)	0.087	0.29 (0.22-0.37)	<0.001**
Croup	11.47 (2.77-47.46)	0.001*	2.08 (1.58-2.74)	<0.001**	1.06 (0.81-1.39)	0.678
Pneumonia	1.54 (0.53-4.53)	0.428	0.16 (0.09-0.30)	<0.001**	0.05 (0.03-0.09)	<0.001**

OR = odds ratio, CI = confidence interval, NA = not applicable. Infinite odds appear when prevalence of a group was 0. Data were adjusted for age and gender.

* $p < 0.016$, ** $p < 0.001$. Bonferroni adjustment applied.