













RESEARCH ARTICLE



## Severity of SARS-CoV-2 Omicron BA.2 infection in unvaccinated hospitalized children: comparison to influenza and parainfluenza infections

Winnie W.Y. Tso <sup>a,b,\*</sup>, Mike Y.W. Kwan <sup>c\*</sup>, Yu Liang Wang<sup>a</sup>, Lok Kan Leung<sup>a</sup>, Daniel Leung <sup>a</sup>, Gilbert T. Chua <sup>a</sup>, Patrick Ip <sup>a</sup>, Daniel Y.T. Fong <sup>d</sup>, Wilfred H.S. Wong <sup>a</sup>, Sophelia H.S. Chan <sup>a</sup>, Jasper F.W. Chan <sup>e</sup>, Malik Peiris <sup>f</sup>, Yu Lung Lau <sup>a†</sup> and Jaime S. Rosa Duque <sup>a†</sup>

<sup>a</sup>Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, People's Republic of China; <sup>b</sup>State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, People's Republic of China; <sup>c</sup>Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong, People's Republic of China; <sup>d</sup>School of Nursing, The University of Hong Kong, Hong Kong, People's Republic of China; <sup>e</sup>State Key Laboratory of Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, The University of Hong Kong, Hong Kong, People's Republic of China; <sup>f</sup>School of Public Health, The University of Hong Kong, Hong Kong, People's Republic of China

### ABSTRACT

There has been a rapid surge of hospitalization due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants globally. The severity of Omicron BA.2 in unexposed, unvaccinated, hospitalized children is unknown. We investigated the severity and clinical outcomes of COVID-19 infection during the Omicron wave in uninfected, unvaccinated hospitalized children and in comparison with influenza and parainfluenza viral infections. This population-based study retrieved data from the HK territory-wide CDARS database of hospitalisations in all public hospitals and compared severe outcomes for the Omicron BA.2-dominant fifth wave (5–28 February 2022,  $n = 1144$ ), and influenza and parainfluenza viruses (1 January 2015–31 December 2019,  $n = 32212$  and  $n = 16423$ , respectively) in children 0–11 years old. Two deaths (0.2%) out of 1144 cases during the initial Omicron wave were recorded. Twenty-one (1.8%) required PICU admission, and the relative risk was higher for Omicron than influenza virus ( $n = 254$ , 0.8%, adjusted RR = 2.1, 95%CI 1.3–3.3,  $p = 0.001$ ). The proportion with neurological complications was 15.0% ( $n = 171$ ) for Omicron, which was higher than influenza and parainfluenza viruses ( $n = 2707$ , 8.4%, adjusted RR = 1.6, 95%CI 1.4–1.9 and  $n = 1258$ , 7.7%, adjusted RR = 1.9, 95%CI 1.6–2.2,  $p < 0.001$  for both, respectively). Croup occurred for Omicron ( $n = 61$ , 5.3%) more than influenza virus ( $n = 601$ , 1.9%, adjusted RR = 2.0, 95%CI 1.5–2.6,  $p < 0.001$ ) but not parainfluenza virus ( $n = 889$ , 5.4%). Our findings showed that for hospitalized children who had no past COVID-19 or vaccination, Omicron BA.2 was not mild. Omicron BA.2 appeared to be more neuropathogenic than influenza and parainfluenza viruses. It targeted the upper airways more than influenza virus.





**ARTICLE HISTORY** Received 2 May 2022; Revised 2 June 2022; Accepted 19 June 2022

**KEYWORDS** Covid-19; omicron; neurological; respiratory; children

### Introduction


During the pre-vaccination era of Coronavirus disease 2019 (COVID-19), 2,128,587 of 72.8 million children in the United States (US) were infected by the wild-type SARS-CoV-2 in the first year of the pandemic[1,2]. Since then, other variants, such as Alpha, Beta, Gamma and Delta also swept across the globe[3–12]. Many who survived developed immunity across SARS-CoV-2 strains[13–15]. Therefore, the severity of Omicron in hospitalized children previously unexposed to COVID-19 is unknown [16,17].

The setting in Hong Kong (HK) can provide a prototypical platform for understanding the severity of Omicron in children. 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[18–22]. These measures were associated with lowest numbers of COVID-19 (an infection rate of ~1% of the population of HK as of 31 October 2021) and near disappearance of influenza and parainfluenza viral infections in HK [23,24]. Furthermore, COVID-19 vaccines were only

**CONTACT** Jaime S. Rosa Duque  [jsrduque@hku.hk](mailto:jsrduque@hku.hk)  Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, People's Republic of China State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, People's Republic of China; Yu Lung Lau  [laulylung@hku.hk](mailto:laulylung@hku.hk)  Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong, People's Republic of China

\*denotes co-first authors who contributed equally

†denotes all corresponding authors who contributed equally

 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/22221751.2022.2093135>.

© 2022 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

approved for HK children aged 5–11 years old in mid-January 2022, so these children remained both uninfected and unvaccinated by the start of the Omicron wave[25]. The emergence of Omicron, predominantly BA.2 in HK, led to exponential increases of SARS-CoV-2 infections during the fifth wave of COVID-19 [23,26]. Indeed, although more children than older adults had experienced favorable outcomes when infected by pre-Omicron SARS-CoV-2, recent studies suggested disproportionately higher hospitalization rates in children after the emergence of Omicron [27,28]. Furthermore, these cases had a greater prediction for more severe complications affecting the neurological and respiratory systems[15,29–32]. In an observational study of the first Omicron wave, likely predominated by the BA.1 sublineage, the most frequent clinical diagnoses linked to pediatric hospitalization was seizure[15]. Other studies suggested that laryngotracheobronchitis, or croup, is more prevalent, severe and prolonged with Omicron than other variants[30–32]. Deaths in children infected with Omicron have occurred but were related to complex underlying co-pathologies[15]. Such emerging data are reshaping the notion that Omicron is possibly not as mild as initially speculated[33].

This population-based study aimed to describe Omicron BA.2-dominant fifth wave's severe clinical outcomes that included mortality, pediatric intensive care unit (PICU) admissions, neurological and respiratory complications in hospitalized children aged 0–11 years, who basically lack immune exposure to past COVID-19 infections or vaccination. Additionally, we compared these severe complication outcomes in the hospitalized children of this age group during this fifth wave of COVID-19 to influenza and parainfluenza viruses from 2015–2019, which commonly caused seizures and croup, respectively[24].

## Methods

### *Study design and patient groups*

We conducted a population-based cohort study of hospitalized children 0–11 years old in HK by analyzing 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. The database has been used for many high-quality, population-based studies with accurate coding[34]. CDARS captures essentially all patient diagnoses the 5 years before and during the COVID-19 pandemic.

During the first 4 waves of the COVID-19 pandemic in HK that predated the Omicron, almost all infected children, regardless of disease severity, were admitted to public hospitals according to the

government's isolation policy[35]. However, during the Omicron wave, due to the overwhelming number of infected cases, children with moderate to severe diseases were admitted to public hospitals for disease management while others remained home. Most children infected with influenza or parainfluenza viruses with moderate to severe diseases before the COVID-19 pandemic, especially those requiring pediatric intensive care unit (PICU), were also admitted to public hospitals, which had a similar practice as the Omicron wave.

This study describes the clinical severity of Omicron in hospitalized children. Additionally, severe outcomes that included neurological and respiratory complications of hospitalized children with COVID-19 during the Omicron wave were compared with those who had influenza and parainfluenza viral infections. Due to differences in the triage criteria for hospital admission during the first 4 waves and the low sample size, outcomes during the first 4 waves (between 1 January 2020 and 1 November 2021) are shown as separate supplementary files only (Supplementary Table 5).

Data were retrieved from CDARS using ICD-9 diagnostic codes (Supplementary Table 1). The study period for the Omicron fifth wave was 5 February to 28 February 2022. Mortality information published by the Centre for Health Protection (CHP) of the HK Government was counterchecked for reference only, which were not included in the final analyses [36]. Hospitalized influenza and parainfluenza viral infections between 1 January 2015 and 31 December 2019 were obtained.

The inputted ICD-9 coding was based on diagnoses of infections by the specific viruses according to 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. Children with the principal diagnoses of COVID-19 or COVID-19-related symptoms/conditions, e.g. seizures, croup, upper respiratory tract infection, gastroenteritis, etc., with a co-diagnosis of COVID-19 or chronic diseases, e.g. cancers, chronic kidney diseases, etc., who were particularly prone to have COVID-19-related illnesses, were regarded as admission due to COVID-19 infection. Cases with co-infections of 2 or more respiratory viruses/SARS-CoV-2 were excluded.

We extracted and categorized data according to the following outcomes:

- A. Mortality and severe complications:
  1. Number of death cases
  2. Pediatric 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 consistent with actual clinical needs for intensive/critical care were counted. Additional data including the child's demographic details were extracted for statistical analyses.

This study was approved by the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HKW IRB UW 22-204) and the Kowloon West Cluster Research Ethics Committee Institutional Review Boards (KWC-REC KW/FR-20-086 (148-10)).

### Statistical analysis

To compare the specified outcomes (dependent variables) between hospitalized cases with Omicron BA.2, influenza and parainfluenza infections (independent variables), a quasi-Poisson regression was conducted to estimate the corresponding relative risks (RRs). Both the crude and adjusted estimates for age, sex and comorbidities (potential confounding independent variables) were obtained. We selected co-morbid conditions that were relevant to this age group according to the pediatric co-morbidity index[37]. To further assess the potential for seasonality influences, we repeated the quasi-Poisson regression on the subgroup of influenza seasons, January-April and July-August, which detected no difference between the main analysis and the subgroup analysis accounting for seasonality (Supplementary Table 4)[38]. To explore the potential influence of age, subgroup analyses were performed for children ages between 0–5 years and 6–11 years (Supplementary Tables 2a, 2b and 3), and their differences were assessed by age interaction. All estimates were accompanied by 95% confidence intervals (CIs), and the statistical tests used a 5% nominal level of significance. The statistical analyses were conducted in R 4.1.3 (R Core Team, Vienna, Austria.).

## Results

### Hospitalization due to covid-19 and other viral infections

1144 children aged 0–11 years were hospitalized during the Omicron wave from 5 February to 28 February 2022 (Table 1). There were 918 (80.2%) aged 0–5 years (Supplementary Tables 2a and 2b). For all other viruses, 32,212 children were hospitalized due to influenza (75.5% aged 0–5 years) and 16423 children due to parainfluenza viral infections (93.0% aged 0–5 years).

### Mortality due to covid-19 and other viruses

Amongst the 1144 Omicron cases, 2 COVID-19-associated deaths were identified (Table 1). In addition, CHP reported 2 other deaths during the study period. They were 11 months, 3, 4 and 9 years old. Three had good past health. The 9-year-old child had Duchenne muscular dystrophy. None were vaccinated against COVID-19. The cause of death for 2 cases was neurological: one with encephalopathy and the other with fulminant cerebral oedema, which recently became a recognized phenotype of encephalitis<sup>27</sup>. Only 2 deaths due to Omicron were used for comparison with other viruses so that all information between groups were equally obtained from CDARS. The number of death due to Omicron was 2 out of 1144 (0.2%), and the adjusted relative risk of death was higher than parainfluenza virus (7 out of 16423, 0.04%; adjusted RR = 4.7, [95% CI (1.1–19.6)],  $p = 0.035$ ) but not influenza virus (16 out of 32,212, 0.1%; adjusted RR = 2.7, [95% CI 0.5–15.7],  $p = 0.257$ ) (Table 2).

### PICU admission due to covid-19 and other viral infections

Twenty-one (1.8%) children with COVID-19 infection required PICU admission during the Omicron wave (Table 1). 254 (0.8%) children with influenza and 270 (1.6%) children with parainfluenza viruses required PICU admission over the 5-year study period. The adjusted RRs of PICU admission for Omicron were higher than influenza virus (adjusted RR = 2.1, [95% CI 1.3–3.3],  $p = 0.001$ ) but similar to parainfluenza virus (Table 2). The risk of Omicron for PICU admission compared to influenza virus in children aged 6–11 years was higher than the younger age group (Supplementary Table 3). Eight (0.7%) children with Omicron required mechanical ventilation, which was higher than influenza virus ( $n = 82$ , 0.3%, adjusted RR = 2.3, [95% CI 1.1–4.9],  $p = 0.03$ ) and similar to parainfluenza virus ( $n = 106$ , 0.7%). Eleven (1.0%) had oxygen use, which was higher than influenza virus ( $n = 120$ , 0.4%, adjusted RR = 2.3,

**Table 1** . Clinical characteristics of all hospital admissions between Omicron BA.2 and influenza and parainfluenza viral infections.

	SARS-CoV-2: Omicron BA.2 (n = 1144)	Influenza (n = 32212)	<i>p</i> -value <sup>†</sup> (Omicron vs Influenza)	Parainfluenza (n = 16423)	<i>p</i> -value <sup>†</sup> (Omicron vs Parainfluenza)
Data period, day/month/year	05/02/2022–28/02/ 2022	01/01/2015–31/12/ 2019		01/01/2015–31/12/ 2019	
Sex					
Male	658 (57.5%)	17504 (54.3%)	0.04*	9228 (56.2%)	0.39
Female	486 (42.9%)	14708 (45.7%)		7159 (43.8%)	
Age mean in years (SD)	3.4 (3.1)	4.1 (2.8)	<0.001***	2.6 (2.1)	<0.001***
0–5 years old	918 (80.2%)	24334 (75.5%)		15268 (93.0%)	
6–11 years old	226 (19.8%)	7878 (24.5%)		1155 (7.0%)	
Comorbidities	71 (6.2%)	1592 (4.9%)	0.06	1393 (8.5%)	0.008**
Mortality and severe complications					
Death cases	2 (0.2%) <sup>‡</sup>	16 (0.1%)		7 (0.04%)	
PICU admissions	21 (1.8%)	254 (0.8%)		270 (1.6%)	
Mechanical ventilation	8 (0.7%)	82 (0.3%)		106 (0.7%)	
Oxygen use	11 (1.0%)	120 (0.4%)		225 (1.4%)	
Neurological complications	171 (15.0%)	2707 (8.4%)		1258 (7.7%)	
All seizures	166 (14.5%)	2650 (8.2%)		1248 (7.6%)	
Febrile seizures	133 (11.6%)	2303 (7.2%)		1142 (7.0%)	
Seizures with fever	28 (2.5%)	290 (1.0%)		42 (0.3%)	
Breakthrough seizures with epilepsy	5 (0.4%)	57 (0.2%)		64 (0.4%)	
Encephalitis/encephalopathy	5 (0.4%)	78 (0.2%)		17 (0.1%)	
Respiratory complications	70 (6.1%)	2343 (7.3%)		2891 (17.6%)	
Croup	61 (5.3%)	601 (1.9%)		889 (5.4%)	
Pneumonia	10 (0.9%)	1756 (5.5%)		2030 (12.4%)	
Croup/pneumonia ratio	6.10	0.34		0.44	

Data are n (%) unless otherwise specified. PICU = paediatric intensive care units.

\**p* < 0.05,

\*\**p* < 0.01,

\*\*\**p* < 0.001.

<sup>†</sup>Fisher's Exact test was used when comparing binary variables, independent t-test was used when comparing two continuous variables.

<sup>‡</sup>Two deaths were extracted from CDARS. During this study period, 4 total deaths were recorded by the Centre for Health Protection, Hong Kong, since these 2 deaths occurred in the Accident & Emergency Department and therefore were not inputted into CDARS by the admitted in-patient wards.

[95% CI 1.2–4.2], *p* = 0.009) but not parainfluenza virus (n = 225, 1.4%).

### Neurological complications due to covid-19 and other viruses

171 (15.0%) children with neurological complications were hospitalised during the Omicron-dominant wave (Table 1). The most common neurological complication was febrile seizure (n = 133, 11.6%), followed by seizure with fever (n = 28, 2.5%). Five (0.4%) had COVID-associated encephalitis/encephalopathy.

The adjusted relative risk of all seizure types in children with Omicron was higher than children with influenza (n = 2650, 8.2%, adjusted RR = 1.6, [95% CI 1.4–1.9], *p* < 0.001) and parainfluenza viruses (n = 1248, 7.6%, adjusted RR = 1.9, [95% CI 1.6–2.2], *p* < 0.001). The seizure RR of Omicron compared to influenza or parainfluenza viruses was higher in children aged 6–11 years than the younger age group (*p* = 0.37 and *p* = 0.042 respectively) (Supplementary Table 3). There were more febrile seizures among Omicron infected children (n = 133, 11.6%) than influenza (n = 2303, 7.2%, adjusted RR 1.4, [95% CI 1.2–1.6], *p* < 0.001) or parainfluenza viruses (n = 1142, 7.0% adjusted RR 1.7, [95% CI 1.4–2.0], *p* < 0.001). Children with Omicron had a increased risk of seizure with fever (n = 28, 2.5%) compared to influenza (n = 290, 1.0%, adjusted RR = 3.0, [95% CI

2.1–4.2], *p* < 0.001) or parainfluenza (n = 42, 0.3%, adjusted RR = 4.3, [95% CI 2.4–7.6], *p* < 0.001) viruses (Table 2). Children with Omicron had a increased risk of encephalitis/encephalopathy (n = 5, 0.4%) compared to parainfluenza virus (n = 17, 0.1%, adjusted RR = 5.3, [95% CI 1.6–17.9], *p* = 0.007), but not influenza virus (n = 78, 0.2%).

### Respiratory complications due to covid-19 and other viruses

Sixty-one (5.3%) with Omicron developed croup, which was higher than influenza (n = 601, 1.9%, adjusted RR = 2.0, [95% CI 1.5–2.6], *p* < 0.001), but not parainfluenza (n = 889, 5.4%) viruses (Tables 1 and 2). The proportions of pneumonia during the Omicron-dominant wave (n = 10, 0.9%) were lower than either influenza or parainfluenza viruses (n = 1756, 5.5%, adjusted RR = 0.2, 95% CI 0.1–0.3 and n = 2030, 12.4%, adjusted RR = 0.1, 95% CI 0.03–0.1, *p* < 0.001 for both, respectively) (Table 2).

## Discussion

This is the first population-based cohort study of hospitalized children that describes the severe clinical manifestations of Omicron BA.2. Additionally, this study found that severe outcomes due to Omicron BA.2 were not less than influenza and parainfluenza

**Table 2.** Relative risks of complications for Omicron BA.2 in comparison to influenza and parainfluenza viral infections.

	SARS-CoV-2 Omicron BA.2 vs Influenza				SARS-CoV-2 Omicron BA.2 vs Parainfluenza			
	Crude		Adjusted <sup>+</sup>		Crude		Adjusted <sup>+</sup>	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Severe complications								
Death cases	3.5 (0.8–15.3)	0.09	2.7 (0.5–15.7)	0.26	4.1 (0.9–19.7)	0.08	4.7 (1.1–19.6)	0.04*
PICU admissions	2.3 (1.5–3.6)	<0.001***	2.1 (1.3–3.3)	0.001**	1.1 (0.7–1.7)	0.62	1.2 (0.8–1.9)	0.37
Mechanical ventilation	2.7 (1.3–5.7)	0.006**	2.3 (1.1–4.9)	0.03*	1.1 (0.5–2.2)	0.83	1.3 (0.6–2.6)	0.55
Oxygen use	2.6 (1.4–4.8)	0.003**	2.3 (1.2–4.2)	0.009**	0.7 (0.4–1.3)	0.25	0.8 (0.4–1.4)	0.40
Neurological complications	1.8 (1.5–2.1)	<0.001***	1.6 (1.4–1.9)	<0.001***	2.0 (1.7–2.3)	<0.001***	1.9 (1.6–2.2)	<0.001***
All seizures	1.8 (1.5–2.0)	<0.001***	1.6 (1.4–1.9)	<0.001***	1.9 (1.6–2.2)	<0.001***	1.9 (1.6–2.2)	<0.001***
Febrile seizures	1.6 (1.4–1.9)	<0.001***	1.4 (1.2–1.6)	<0.001***	1.7 (1.4–2.0)	<0.001***	1.7 (1.4–2.0)	<0.001***
Seizures with fever	2.7 (1.8–4.0)	<0.001***	3.0 (2.1–4.2)	<0.001***	9.6 (5.9–15.4)	<0.001***	4.3 (2.4–7.6)	<0.001***
Breakthrough seizures with epilepsy	2.5 (1–6.2.0)	0.05	NA	NA	1.1 (0.5–2.8)	0.81	NA	NA
Encephalitis/ encephalopathy	1.8 (0.7–4.5)	0.20	1.8 (0.8–4.2)	0.17	4.2 (1.6–11.4)	0.005**	5.3 (1.6–17.9)	0.007**
Respiratory complications	0.8 (0.7–1.1)	0.14	0.8 (0.7–1.0)	0.09	0.3 (0.3–0.4)	<0.001***	0.3 (0.3–0.4)	<0.001***
Croup	2.9 (2.2–3.7)	<0.001***	2.0 (1.5–2.6)	<0.001***	1.0 (0.8–1.3)	0.91	1.0 (0.8–1.3)	0.74
Pneumonia	0.2 (0.1–0.3)	<0.001***	0.2 (0.1–0.3)	<0.001***	0.1 (0.03–0.1)	<0.001***	0.1 (0.03–0.1)	<0.001***

RR = relative risk, CI = confidence interval.

<sup>+</sup>Model was adjusted by age, sex and comorbidities.\* $p < 0.05$ ,\*\* $p < 0.01$ ,\*\*\* $p < 0.001$ .

NA = not applicable as epilepsy is a co-morbid condition

viruses. There was a higher risk of death from Omicron BA.2 than parainfluenza virus, and Omicron BA.2 was more pathogenic than influenza virus, resulting in more PICU admissions, mechanical ventilation and oxygen use. Omicron BA.2 was neuro-pathogenic, as patients had more seizures than influenza and parainfluenza infections. Importantly, the risks of encephalitis/encephalopathy were higher for Omicron BA.2 than parainfluenza virus. Omicron BA.2 caused more disease in the upper airway compared to influenza virus but less pneumonia.

Our study confirms previous findings from South Africa that the Omicron variant might be associated with increased seizure risks<sup>8</sup>. Prior to the Omicron outbreak, seizure was not a common manifestation of pediatric COVID-19[38,39]. Since the Omicron surge, 15.0% of hospitalized children with COVID-19 were admitted due to neurological complications compared to the 3.8% reported for other SARS-CoV-2 variants during the pre-vaccinated era in the UK[40]. A majority (80%) were simple febrile seizure, but 17% of seizures were out of its typical diagnostic age range. The risks of seizure for Omicron BA.2 from this study was 1.6–1.9 more than influenza and parainfluenza viruses. The risks of seizure with fever in children aged  $\geq 6$  years were even higher, at 3–4 times higher than influenza and parainfluenza viruses. In view of the 2 deaths related to COVID-associated encephalitis/encephalopathy, it will be important for pediatricians to anticipate such complication, in particular, how to differentiate acute encephalitis from febrile seizure and initiate medical interventions promptly.

Recently, croup due to Omicron has been described to be more severe and persistent[30,32]. Omicron had replaced parainfluenza as the predominant cause of viral croup during the initial phase of the Omicron

variant surge according to a small study in the US, where the incidence of croup due to Omicron had doubled[30,31]. These patients were more likely to require nebulized epinephrine[30]. In HK, there was a >2-fold increase in croup for Omicron BA.2 than influenza, while similar to parainfluenza. This observation that Omicron preferentially affects the upper airway is supported by *ex vivo* human lung cultures demonstrating Omicron replicates better in the bronchus than lungs[41].

Our finding that Omicron BA.2 is associated with severe hospital outcomes in children was consistent with a recent age-specific analysis of hazard ratio (HR) of hospital admissions in England with Omicron BA.1 compared with Delta[42]. 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, so that 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. In parallel, the 2 in-hospital deaths from our study were <5 years old.

Possible explanations as to why hospitalized children with Omicron BA.2 in HK have such clinical complications could be related to their low exposure to previous COVID-19 variants due to the strict social-distancing practices[5]. The effectiveness of such measures is substantiated by the near-complete disappearance of some communicable diseases, including influenza and parainfluenza viruses, in the

HK community since early 2020[24]. Furthermore, the vaccination rate, especially in young children, was extremely low at the beginning of the Omicron surge. As of 12 February 2022, only 6% of children age 5–11 years had received their 1st dose of vaccination[25]. Therefore, it is possible that unexposed, unvaccinated, hospitalized children are more vulnerable due to their lack of cross-reactive immunity, in particular, the more durable and broader T cell immunity[43–45].

This study had limitations. First, genomic sequencing information is not encoded in CDARS, so not all included COVID-19 cases were caused by Omicron BA.2. However, based on epidemiological data, even at the start of the fifth wave, Omicron had become the dominant strain, accounting for >60% of the total cases[46]. CHP reported that out of the 130 COVID-associated deaths 3 February to 2 March 2022 with available genome sequencing results, 117 were Omicron and only 13 were Delta[47]. Since epidemiological criteria to describe the type of SARS-CoV-2 infection do not provide certainty on Omicron BA.2, future research can be enriched by completion of genomic sequencing results for all participants. Second, we caution our in-hospital mortality of 0.2%, which does not reflect the overall deaths in the community because some children with mild COVID-19 during the Omicron wave were not admitted, and CHP reported 0.02% case-fatality rate (CFR) for 0–9 years old children at the time of this writing on 15 March 2022[48]. However, this information emphasizes that clinicians should anticipate potential deterioration for hospitalized pediatric patients as they are at risk of severe outcomes. Third, the comparison of Omicron with influenza and parainfluenza viruses were made from disjoint time periods. During January 2020 to February 2022, almost all children with COVID-19 were hospitalized in public hospitals and facilities only, whereas for children infected with influenza or parainfluenza viruses, they had the option of in-hospital care in the public or the private sector. Nevertheless, based on our clinical experience, there were no major calendar-period-specific changes in nasopharyngeal testing practices or overall healthcare-seeking behaviors of HK parents when their child became acutely ill. Furthermore, official statistics showed CDARS accounted for 85% of all hospitalization in HK[49]. Even in the pre-COVID-era, almost all children with serious neurological or respiratory compromise were transferred to public hospitals due to the lack of pediatric intensive care support in the private sector. These factors limit potential underestimation of severe influenza and parainfluenza-related complications. Fourth, we were unable to perform extensive analyses for the first 4 waves of COVID-19 because of its low sample size in HK even as CDARS should have captured

essentially all these cases that required admission to public hospitals under HK Government's isolation policies. Finally, information on the influenza virus infection by type/subtypes or vaccination status was unavailable for all individual patients in this study, precluding data analyses on the effects of these potential factors. Recent publications from our group and CHP demonstrated that during the study period of 2015–2019, the predominant influenza viruses in HK were H1N1, H3N2 and B in HK, which varied by month[38,50,51]. Moreover, although the HK community of children had 12% influenza vaccine uptake in 2015 to recently up to 69.2% for those attending primary schools enrolled in the vaccination scheme that began in 2018, the vaccination rates had been merely 8–12% for children who were hospitalised[38,50–52]. For clearer delineation between the severity of the 2 viruses, further research specifically comparing COVID-19 with those who had been uninfected and unvaccinated with the influenza virus only will be required. The strengths of this study included the large sample size of the study design that allowed for controlling confounders such as age, sex, co-morbidities and influenza seasonality. Additionally, these study data were reviewed by bioinformatics statisticians, physicians and a virologist with a spectrum of subspecialty expertise to assure relevant clinical implication of disease complications.

In conclusion, Omicron BA.2 can cause severe disease in unvaccinated, hospitalized children who had low exposure to coronaviruses the past 2 years. As many studies have demonstrated COVID-19 vaccination efficacy in reducing severe complications and deaths[53], it is necessary to advocate for immunization access, particularly for vulnerable children as recommended by major health organizations, to minimize vaccine-preventable diseases[54–60].

## Contributors

W.W.Y. Tso, J.S. Rosa Duque, Y.L. Lau and M.Y.W. Kwan conceptualized the study. W.W.Y. Tso, J.S. Rosa Duque, Y.L. Lau, W.H.S. Wong and Y.L. Wang designed the study. W.W.Y. Tso and P. Ip provided funding. J.S. Rosa Duque and Y.L. Lau supervised the project. W.W.Y. Tso, J.S. Rosa Duque, Y.L. Wang, L.K. Leung, M.Y.W. Kwan and G.T. Chua led the study administrative procedures. Y.L. Wang and W.H.S. Wong provided software support. W.W.Y. Tso, Y.L. Wang, L.K. Leung and M.Y.W. Kwan retrieved and reviewed the patient records. W.W.Y. Tso, J.S. Rosa Duque, Y.L. Lau, M.Y.W. Kwan, S.H.S. Chan and J.F.W. Chan provided clinical interpretation of the patient records and results. Y.L. Wang, L.K. Leung, W.W.Y. Tso, J.S. Rosa Duque and W.H.S. Wong curated the data. W.W.Y. Tso, J.S. Rosa Duque, W.H.S. Wong, D.Y.T. Fong, Y.L. Wang, L.K. Leung and D. Leung analysed the data. Y.L. Wang, W.W.Y. Tso and L.K. Leung visualised the data. Y.L. Wang, L.K. Leung, W.W.Y. Tso, J.S. Rosa

Duque and W.H.S. Wong validated the data. W.W.Y. Tso and M.Y.W. Kwan wrote the first draft as supervised by J.S. Rosa Duque and Y.L. Lau, with input from W.H.S. Wong, D.Y.T. Fong, D. Leung, J.F.W. Chan, S.H.S. Chan and M. Peiris. All authors reviewed and approved the final 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. The R script for performing the main statistical analysis of this paper is shown in the Supplementary Appendix.

### 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.













### Disclosure statement

No potential conflict of interest was reported by the author (s).

### Funding

This study was supported by the Hong Kong Research Grants Council Collaborative Research Fund (C7149-20G) and Seed Funding for Basic Research of the University of Hong Kong (202111159117).

### ORCID

Winnie W.Y. Tso  <http://orcid.org/0000-0002-5859-015X>  
 Mike Y.W. Kwan  <http://orcid.org/0000-0002-1476-9625>  
 Daniel Leung  <http://orcid.org/0000-0002-9360-6233>  
 Gilbert T. Chua  <http://orcid.org/0000-0003-0333-0059>  
 Patrick Ip  <http://orcid.org/0000-0002-6797-6898>  
 Daniel Y.T. Fong  <http://orcid.org/0000-0001-7365-9146>  
 Wilfred H.S. Wong  <http://orcid.org/0000-0001-8396-2368>  
 Sophelia H.S. Chan  <http://orcid.org/0000-0002-2990-0163>  
 Jasper F.W. Chan  <http://orcid.org/0000-0001-6336-6657>  
 Malik Peiris  <http://orcid.org/0000-0001-8217-5995>  
 Yu Lung Lau  <http://orcid.org/0000-0002-4780-0289>  
 Jaime S. Rosa Duque  <http://orcid.org/0000-0002-5292-5510>

### References

- [1] American Academy of Pediatrics. Children's hospital association. Children and COVID-19: State Data Report. 2022.
- [2] ChildStats.gov. Child population: Number of children (in millions) ages 0–17 in the United States by age, 1950–2020 and projected 2021–2050 2020 [cited 2022 6 April]. Available from: <https://www.childstats.gov/americaschildren/tables/pop1.asp>.
- [3] Sinha IP, Harwood R, Semple MG, et al. COVID-19 infection in children. *Lancet Respir Med.* 2020;8(5):446–447.
- [4] US Centers for Disease Control and Prevention. Hospitalization of infants and children aged 0–4 years with laboratory-confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022, <https://www.cdc.gov/mmwr/volumes/71/wr/mm7111e2.htm>. *Morbidity and Mortality Weekly Report (MMWR)*. 2022.
- [5] Tso WWY, Wong RS, Tung KTS, et al. Vulnerability and resilience in children during the COVID-19 pandemic. *Eur Child Adolesc Psychiatry.* 2022;31(1):161–176.
- [6] Flor LS, Friedman J, Spencer CN, et al. Quantifying the effects of the COVID-19 pandemic on gender equality on health, social, and economic indicators: a comprehensive review of data from march, 2020, to September, 2021. *Lancet.* 2022 Mar 2.
- [7] Crotty S. Hybrid immunity. *Science.* 2021;372(6549):1392–1393.
- [8] Walls AC, Sprouse KR, Bowen JE, et al. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. *Cell.* 2022;185(5):872–880.e3.
- [9] Abdullah F, Myers J, Basu D, et al. Decreased severity of disease during the first global omicron variant COVID-19 outbreak in a large hospital in tshwane, South Africa. *Int J Infect Dis.* 2022;116:38–42.
- [10] Brandal LT, MacDonald E, Veneti L, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. *Euro Surveill.* 2021;26(50).
- [11] Christensen PA, Olsen RJ, Long SW, et al. Signals of significantly increased vaccine breakthrough, decreased hospitalization rates, and less severe disease in patients with coronavirus disease 2019 caused by the Omicron variant of severe acute respiratory syndrome coronavirus 2 in houston, texas. *Am J Pathol.* 2022;192(4):642–652.
- [12] Houhamdi L, Gautret P, Hoang VT, et al. Characteristics of the first 1119 SARS-CoV-2 Omicron variant cases, in marseille, France, November–December 2021. *J Med Virol.* 2022;94(5):2290–2295.
- [13] Wang L, Berger NA, Kaelber DC, et al. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of omicron. *medRxiv.* 2022 Jan 2.
- [14] Wang L, Berger NA, Kaelber DC, et al. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. *medRxiv.* 2022 Jan 13.
- [15] Cloete J, Kruger A, Masha M, et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. *Lancet Child Adolesc Health.* 2022 Feb 18.

- [16] Bhattacharyya RP, Hanage WP. Challenges in inferring intrinsic severity of the SARS-CoV-2 Omicron variant. *N Engl J Med.* 2022;386(7):e14.
- [17] Lavine JS, Bjornstad ON, Antia R. Immunological characteristics govern the transition of COVID-19 to endemicity. *Science.* 2021;371(6530):741–745.
- [18] Letter to Schools on “Arrangements on deferral of class resumption for all schools” (13 February 2020) [Internet]. 2020; 13 February [cited 10 May 2021]. [https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb\\_20200213\\_eng.pdf](https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb_20200213_eng.pdf).
- [19] Arrangements of Early Commencement of Summer Holiday for All Schools [Internet]. (2020). 10 July [cited 10 May 2021]. [https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb\\_20200505\\_eng.pdf](https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb_20200505_eng.pdf).
- [20] Continuation of Suspension of Face-to-Face Classes for Schools in Hong Kong: The Arrangements [Internet]. (2021). 4 January [cited 10 May 2021]. [https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb\\_20210104\\_eng.pdf](https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb_20210104_eng.pdf).
- [21] Suspension of face-to-face classes of primary schools, kindergartens and kindergarten-cum-child care centres until Chinese New Year [Internet]. 2022; 11 January [cited 14 March 2022]. <https://www.info.gov.hk/gia/general/202201/11/P2022011100677.htm>.
- [22] Letter to Kindergartens / Kindergarten-cum-Child Care Centres on “Arrangement of Special Vacation in the 2021/22 School Year” [Internet]. 2022; 28 February [cited 14 March 2022]. [https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb\\_20220228\\_eng\\_d.pdf](https://www.edb.gov.hk/attachment/en/sch-admin/admin/about-sch/diseases-prevention/edb_20220228_eng_d.pdf).
- [23] HK Centre for Health Protection. Statistics. <https://www.chp.gov.hk/en/static/24012.html#>. 2022;2022.
- [24] HK Centre for Health Protection. Detection of pathogens from respiratory specimens. <https://www.chp.gov.hk/en/statistics/data/10/641/642/2274.html>. 2022.
- [25] HK Centre for Health Protection. COVID-19 Vaccination Programme. <https://www.covidvaccine.gov.hk/en/dashboard>. 2022;2022(12 February).
- [26] Cheng VC, Ip JD, Chu AW, et al. Rapid spread of SARS-CoV-2 Omicron subvariant BA.2 in a single-source community outbreak. *Clin Infect Dis.* 2022 Mar 10.
- [27] Wang L, Berger NA, Kaelber DC, et al. COVID infection rates, clinical outcomes, and racial/ethnic and gender disparities before and after Omicron emerged in the US. *medRxiv.* 2022 Feb 22.
- [28] Marks KJ, Whitaker M, Anglin O, et al. Hospitalizations of children and adolescents with laboratory-confirmed COVID-19 — COVID-NET, 14 states, July 2021–January 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(7):271–278.
- [29] Ludvigsson JF. Convulsions in children with COVID-19 during the Omicron wave. *Acta Paediatr.* 2022 Jan 31.
- [30] Tunc EM, Shin CKJ, Usoro E, et al. Croup during the COVID-19 Omicron variant surge. *medRxiv.* 2022:2022.02.02.22270222.
- [31] Brewster RCL, Parsons C, Laird-Gion J, et al. COVID-19-associated croup in children. *Pediatrics.* 2022 Mar 8.
- [32] Murata Y, Tomari K, Matsuoka T. Children with croup and SARS-CoV-2 infection during the large outbreak of omicron. *Pediatr Infect Dis J.* 2022 Feb 17.
- [33] Robinson ML, Morris CP, Betz J, et al. Impact of SARS-CoV-2 variants on inpatient clinical outcome. *medRxiv.* 2022 Feb 3.
- [34] Sing CW, Woo YC, Lee ACH, et al. Validity of major osteoporotic fracture diagnosis codes in the clinical data analysis and reporting system in Hong Kong. *Pharmacoepidemiol Drug Saf.* 2017;26(8):973–976.
- [35] Chua GT, Wong JSC, Lam I, et al. Clinical characteristics and transmission of COVID-19 in children and youths during 3 waves of outbreaks in Hong Kong. *JAMA Netw Open.* 2021;4(5):e218824.
- [36] HK Centre for Health Protection. <https://www.coronavirus.gov.hk>. Hong Kong 2022.
- [37] Sun JW, Bourgeois FT, Haneuse S, et al. Development and validation of a pediatric comorbidity index. *Am J Epidemiol.* 2021;190(5):918–927.
- [38] HK Centre for Health Protection. Seasonal Influenza. <https://www.chp.gov.hk/en/features/14843.html>. 2021.
- [39] Fink EL, Robertson CL, Wainwright MS, et al. Prevalence and risk factors of neurologic manifestations in hospitalized children diagnosed with acute SARS-CoV-2 or MIS-C. *Pediatr Neurol.* 2022;128:33–44.
- [40] Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. *Lancet Child Adolesc Health.* 2021;5(9):631–641.
- [41] Hui KPY, Ho JCW, Cheung MC, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. *Nature.* 2022 Feb 1.
- [42] Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet.* 2022 Mar 16.
- [43] Ng KW, Faulkner N, Cornish GH, et al. Preexisting and de novo humoral immunity to SARS-CoV-2 in humans. *Science.* 2020;370(6522):1339–1343.
- [44] Kundu R, Narean JS, Wang L, et al. Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts. *Nat Commun.* 2022;13(1):80.
- [45] Swadling L, Diniz MO, Schmidt NM, et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. *Nature.* 2022;601(7891):110–117.
- [46] HK Centre for Health Protection. CHP Newsletter, [https://www.chp.gov.hk/files/pdf/chp50\\_en.pdf](https://www.chp.gov.hk/files/pdf/chp50_en.pdf). 2022 (50).
- [47] news.gov.hk. HK sees 25k COVID-19 cases (Chinese Version only) 2022 [updated 7 March 2022; cited 2022 6 April]. Available from: [https://www.news.gov.hk/chi/2022/03/20220307/20220307\\_180507\\_220.html](https://www.news.gov.hk/chi/2022/03/20220307/20220307_180507_220.html).
- [48] HK Centre for Health Protection. Archives of latest situation of cases of COVID-19. <https://www.chp.gov.hk/en/features/102997.html>. 2022.
- [49] Census and Statistics Department of the HKSAR. Hong Kong Annual Digest of Statistics (2021 Edition). Hong Kong 2021.
- [50] Chiu SS, Kwan MYW, Feng S, et al. Influenza vaccine effectiveness against influenza A(H3N2) hospitalizations in children in Hong Kong in a prolonged season, 2016/2017. *J Infect Dis.* 2018;217(9):1365–1371.



- [51] Chiu SS, Kwan MYW, Feng S, et al. Interim estimate of influenza vaccine effectiveness in hospitalised children, Hong Kong, 2017/18. *Euro Surveill.* 2018 Feb;23(8).
- [52] Lau YL, Wong WHS, Hattangdi-Haridas SR, et al. Evaluating impact of school outreach vaccination programme in Hong Kong influenza season 2018 - 2019. *Hum Vaccin Immunother.* 2020;16(4):823–826.
- [53] Luring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *Br Med J.* 2022 Mar 9;376:e069761.
- [54] Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. *N Engl J Med.* 2022 Mar 2.
- [55] Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 COVID-19 vaccine in children 5 to 11 years of Age. *N Engl J Med.* 2022;386(1):35–46.
- [56] Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med.* 2021;385(10):875–884.
- [57] Lau Y-L, Duque JR, Wang X, et al. Immunogenicity and reactogenicity of SARS-CoV-2 mRNA and inactivated vaccines in healthy adolescents. *Nat Commun.* 2022: in press.
- [58] UK Joint Committee on Vaccination and Immunisation (JCVI). JCVI statement on vaccination of children aged 5 to 11 years old. <https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-aged-5-to-11/jcvi-statement-on-vaccination-of-children-aged-5-to-11-years-old>. 2022.
- [59] US Centers for Disease Control and Prevention. COVID-19 vaccines for children and teens. [https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvaccines%2Frecommendations%2Fadolescents.html](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvaccines%2Frecommendations%2Fadolescents.html). 2022.
- [60] International League Against Epilepsy. COVID-19 vaccines and people with epilepsy. <https://www.ilae.org/patient-care/covid-19-and-epilepsy/covid-19-vaccines-and-people-with-epilepsy>. 2022.