

## Distinguishing coronavirus disease 2019 from influenza in children remains challenging

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### Abstract

Clinical descriptions about influenza-like illness in children seem non-specific during the co-circulation of SARS-CoV-2 and influenza. This paper aimed to summarize recent studies comparing clinical features and outcome, laboratory and radiological findings of COVID-19 patients with influenza patients in the paediatric population.

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### To the Editor,

Coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan in the province of Hubei in China. Since then, it has evolved into a worldwide pandemic and became one of the world's toughest health problems, especially in adult patients but also in pediatric population [1–3]. Influenza A and B affect 20%–30% of children annually with most cases occurring during the winter season [4,5]. The 2019–2020 influenza season had a lower than

expected burden, especially in children. This decrease was probably the result of a behavioural or ecological interaction with COVID-19. The occurrence of a syndemic episode with co-circulating influenza virus and SARS-CoV-2 is still an unknown hypothesis. SARS-CoV-2 and influenza virus share similarities, such as viral shedding, route of transmission and clinical presentation in adults and children presenting with influenza-like illness. In October 2020, we published a paper in *Microbes and Infection* describing an observational study of 124 adults comparing clinical features and outcome between COVID-19 and influenza [6]. We showed that regarding demographic characteristics such as age, sex and co-morbidities no differences were found between the two groups. Neurological symptoms (facial headache, anosmia and dysgeusia) and diarrhoea were statistically more frequent in COVID-19 patients. Respiratory symptoms (productive cough and dyspnoea), ocular symptoms (conjunctival hyperaemia and tearing) and vomiting were more frequent with influenza infection [6].

Until now, there have been few studies comparing COVID-19 with influenza in paediatric populations [7–10]. The current paper compares the clinical features and outcomes, and laboratory and radiological findings of children with COVID-19 and those with influenza. In these four studies, all patients were hospitalized. One study compared hospitalized COVID-19 patients with outpatients with influenza [8]. Table 1 summarizes studies of children comparing significant clinical features, and laboratory and radiological findings in COVID-19 and influenza paediatric populations with a value of  $p < 0.05$ . In the study by Song *et al.*, the median age was 8.4 years for COVID-19 patients and 3.9 years for influenza patients. The hospitalization rate was 17.1% for COVID-19 patients and 20.8% for influenza patients [7]. The mean age in the Zhao *et al.* paediatric population was  $5.7 \pm 3.8$  years in 23 hospitalized children with COVID-19, whereas in Li *et al.* the mean age was  $21.8 \pm 16.7$  months in 59 patients infected with influenza A virus [8,10]. Hospitalized children infected with SARS-CoV-2 were older, and had a lower body temperature than those with influenza; however, fever and gastrointestinal symptoms such as vomiting and diarrhoea were more often described (in two of three studies) in influenza patients, and this difference was significant [8,10]. Song *et al.* reported that 65% of children hospitalized with COVID-19 had at least one underlying medical condition versus 42% in those hospitalized with influenza (OR 2.6; 95% CI 1.4–4.7,  $p < 0.002$ ). Neurological issues were the most often identified underlying condition and were present in 20% of patients hospitalized with COVID-19 compared with 8% of patients hospitalized with influenza (OR 2.8; 95% CI 1.3–6.2,  $p < 0.002$ ) [7]. In the paediatric population, symptoms such as fever, diarrhoea or vomiting, were more often described in

**TABLE 1. Significant clinical features, and laboratory and radiological findings in COVID-19 and influenza paediatric populations**

Reference (number of COVID-19/ influenza patients)	Findings type	Significant findings	Hospitalized with COVID-19 (%)	Hospitalized with influenza (%)	OR (95% CI)	p value	
Song et al. [7] (315/1402)	Clinical	Age >15 years	<b>37</b>	6	25.8 (14.2–48.5)	<0.001	
		Fever	<b>76</b>	55	2.6 (1.4–5.1)	0.01	
		Diarrhoea/vomiting	<b>26</b>	12	2.5 (1.2–5.0)	0.01	
		Myalgia	<b>22</b>	7	3.9 (1.8–8.5)	0.001	
		Headache	<b>11</b>	3	3.9 (1.3–11.5)	0.01	
		Chest pain	<b>11</b>	3	3.9 (1.3–11.5)	0.01	
Yang et al. [8] (23/138)	Clinical	Cough duration (days)	2.0 ± 5.2	<b>2.4 ± 3.2</b>	<b>3.8 ± 2.3</b>	<0.05	
		Body temperature (°C)	37.4 ± 1.2	<b>38.3 ± 1.5</b>	<b>39.3 ± 0.9</b>	<0.05	
		Fever duration (days)	1.0 ± 1.4	<b>2.4 ± 3.0</b>	<b>4.0 ± 1.5</b>	<0.05	
		Fever >39.0°C	8.7	<b>37.7</b>	<b>60.9</b>	<0.05	
		Nasal congestion	4.3	<b>31.9</b>	<b>30.4</b>	<0.05	
		Rhinorrhoea	4.3	<b>29.0</b>	<b>27.5</b>	<0.05	
		Sore throat	0.0	<b>37.8</b>	<b>23.2</b>	<0.05	
		Vomiting	0.0	<b>27.5</b>	<b>24.6</b>	<0.05	
		Laboratory	Aspartate aminotransferase (U/L)	<b>37.5 ± 56.1</b>	35.5 ± 72.8	28.6 ± 11.1	<0.001
			Alanine aminotransferase (U/L)	36.3 ± 37.1	<b>46.0 ± 83.7</b>	24.8 ± 9.4	<0.001
	Cholinesterase (U/L)		<b>9477.2 ± 2414.1</b>	6512.7 ± 2085.7	7391.4 ± 1193.5	<0.001	
	CRP (mg/L)		2.2 ± 4.4	<b>48.0 ± 74.8</b>	<b>7.9 ± 9.0</b>	<0.001	
	ESR (mm/h)		9.6 ± 9.8	<b>21.2 ± 18.5</b>	<b>22.2 ± 7.0</b>	0.019	
	Aspartate aminotransferase (U/L, extr)		31.5 (20.35–40.0)	<b>46.5 (36–59.3)</b>	—	<0.001	
	Procalcitonin (ng/l, extr)		0.07 (0.05–0.1)	<b>0.31 (0.09–0.63)</b>	—	0.001	
	Liu et al. [9] (24/67)	Laboratory	Lactate dehydrogenase (U/L)	300.5 (206.0–394.0)	<b>369 (319–467)</b>	—	0.036
			Cough	70.2	<b>98.3</b>	—	<0.001
Fever			54.4	<b>84.7</b>	—	<0.001	
GI symptoms			14.1	<b>35.7</b>	—	0.007	
Severe pneumonia			3.5	<b>18.6</b>	—	0.016	
Lymphocyte (× 10 <sup>9</sup> /L)			<b>4.58 ± 2.06</b>	3.56 ± 2.01	—	0.006	
Leucocytes (× 10 <sup>9</sup> /L)			7.87 ± 2.87	<b>9.89 ± 4.84</b>	—	0.027	
Neutrophils (× 10 <sup>9</sup> /L)			2.43 ± 1.92	<b>5.16 ± 4.46</b>	—	<0.001	
CRP (mg/L)			3.7 ± 6.85	<b>15.1 ± 32.2</b>	—	0.001	
Procalcitonin (mm/h)			0.09 ± 0.09	<b>0.68 ± 1.82</b>	—	<0.001	
Li et al. [10] (57/59)	Clinical	Creatine kinase (U/L)	<b>147 ± 89</b>	130 ± 121	—	0.042	
		D-dimer (ng/mL)	0.34 ± 0.29	<b>1.94 ± 2.88</b>	—	<0.001	
		Prothrombin time (mm/h)	10.8 ± 0.7	<b>11.2 ± 0.8</b>	—	0.014	
		Potassium (mmol/L)	5.14	<b>7.07</b>	—	0.001	
		GGO	<b>42.1</b>	15.0	—	0.032	
	Laboratory	Consolidation	5.2	<b>25.0</b>	—	0.025	
Radiological							

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; extr, extremes; GI, gastrointestinal; GGO, ground-glass opacity.

\*p values for both COVID-19 versus influenza inpatients and COVID-19 versus influenza outpatients.

Bold type indicates illness (COVID-19 or influenza) with significant difference.

hospitalized patients with seasonal influenza than in those with COVID-19 [8,10]. However, Song *et al.* concluded that fever and gastrointestinal symptoms were more often described in children hospitalized with COVID-19. This can be explained by the demographic characteristics of the included patients; 37% were adolescents over 15 years old, who have results similar to those of adults [6]. Currently, it is known that neurological symptoms such as the association of anosmia and dysgeusia can lead to the diagnosis of SARS-CoV-2 infection in patients presenting with influenza-like illness [11]. This is not possible with children who are not going to express their subjective olfactory and gustatory dysfunctions; however, it is necessary to look for new loss of smell and taste in children from a certain age range. Concerning the outcome, no statistically significant difference was found in hospitalization rate, intensive care unit admission

rate and use of mechanical ventilator support between the two groups [7]. These observations were habitually reported in adult studies [6]; however, SARS-CoV-2 and influenza virus affect children less severely than adults [3]. Zhao *et al.* concluded that children with COVID-19 were associated with a higher ratio of in-home infection than influenza inpatients (95.6% versus 21.7%,  $p < 0.001$ ). Milder COVID-19 symptoms in children could be explained by the lower intracellular response induced by angiotensin-converting enzyme 2 in alveolar epithelial cells [8]. Concerning laboratory investigations, three studies of four concluded that children with COVID-19 had higher levels of lymphocytes, creatine kinase, aspartate aminotransferase (AST) and cholinesterase than children with influenza [8,10]. However, Liu *et al.* concluded in a recent paper that children with COVID-19 had statistically lower levels of

procalcitonin, AST and lactate dehydrogenase on univariate analysis; only AST was found to be statistically significant after multivariate analysis [9]. Since the identification of SARS-CoV-2 in children, a European systematic review of 655 children with mild to moderate clinical manifestations of COVID-19 noted lymphopenia or neutropenia in 13% and elevated inflammatory markers in 31% [3]. Laboratory results were comparable to those found in adult patients; COVID-19 patients showed significantly lower levels of leucocytes (especially of neutrophils) and inflammatory markers such as C-reactive protein and procalcitonin, whereas lymphocyte levels were significantly higher compared with influenza patients [10]. In children, imaging results more commonly presented as ground-glass opacities (GGO) in children with COVID-19 under 5 years of age; however, consolidation was more common in influenza patients [10]. In terms of imaging characteristics, only one study compared chest CT scans in this population and reported that GGO were significantly more common in children with COVID-19 than children with influenza [10]. Radiological data showed that GGO, interlobular septal thickening and a peripheral distribution were more common in adult patients with COVID-19 than in patients with influenza. However, consolidation, nodules and linear opacities and pulmonary complications such as pneumomediastinum and pneumothorax were more common in patients with influenza than those with COVID-19 [5]. The scarcity of moderate to severe respiratory forms in children makes the amount of radiological data limited in this population [3].

There are some limitations to our review. COVID-19 is relatively novel with a limited number of patients and studies. In most articles, the clinical features, laboratory data and CT findings reported about influenza dated before the onset of COVID-19. A meta-analysis is recommended to further define the differences and the similarities between COVID-19 and influenza.

This paper provides a comprehensive comparison between children with SARS-CoV-2 and influenza infections, regarding co-morbidities, clinical and paraclinical features and outcome. Clinical manifestations of COVID-19 and influenza seem to be similar with few differences; fever and gastrointestinal symptoms were more often described in children aged <15 years with COVID-19 than in children with influenza. The two viruses seem to provide laboratory abnormalities with no specifics for either of them (only AST level seems to be more elevated in COVID-19 than influenza). Radiological findings showed that GGO were usually more frequent and peripherally located in COVID-19 compared with influenza. All these findings can help paediatric infectious diseases clinicians when dealing with cases of influenza-like illness during

the period of possible co-circulation of influenza and SARS-CoV-2.

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## Authors' contributions

SZ and MO collected the epidemiological and clinical data, and drafted the manuscript. TK, NU, NB and VG revised the final manuscript.

## Conflict of interest

None.

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