



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

The curious case of coronavirus disease 2019 (COVID-19) in children



To the Editor:

The pediatric population has classically been viewed to be highly vulnerable to infectious diseases. Consequently, this cohort deserves diligent observation during an infectious outbreak. The US Centers for Disease Control and Prevention considers children, especially those younger than 5 years of age, as a high-risk category for influenza-related disease.¹ During the last influenza A pandemic (H1N1 2009), 13% of the infected individuals were younger than 5 years.²

The age distribution of patients in the coronavirus disease 2019 (COVID-19) pandemic is incongruent with that of the H1N1 pandemic of 2009. At our tertiary care center, 215 individuals been evaluated for COVID-19 through April 10, 2020. Of those tested, all 22 individuals younger the age of 18 years were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a systematic review of 45 datasets, Ludvigsson found that less than 5% of COVID-19 cases occurred in children younger than 18 years of age.³ Two other novel coronavirus diseases, severe acute respiratory syndrome and Middle East respiratory syndrome, also show similarly low rates of infection in the pediatric population.⁴ Furthermore, retrospective studies to date suggest that children infected with SARS-CoV-2 generally have mild or no symptoms. In a study of 2143 COVID-19 cases in children, disease manifestations were found to be greatest in age younger than 1 year, with a falling trend in severity with increasing age up to 18 years.⁵

A number of hypotheses have been proposed for the relative sparing of children in the COVID-19 pandemic: a more likely stimulus-naïve immune system, immaturity of angiotensin-converting enzyme 2 receptors, and underdeveloped humoral and cellular immune responses resulting in milder inflammation.^{5,6} It also is hypothesized that recurrent viral infections that typify childhood may induce greater or more frequent innate and adaptive responses, such as to leading to greater total immunoglobulin levels that might be protective against a novel virus.⁵

We present the epidemiologic differences among 3 coronavirus diseases (severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19) and the influenza pandemic (H1N1 2009) disease in the [Table](#).^{2-4,6-17} Although we present data about the H1N1 pandemic that were amassed during the decade that has passed since, the landscape of SARS-CoV-2 infection and COVID-19, especially in children, is evolving, and a more mature analysis may unearth a different trend. Although the current figures are encouraging, the true burden of COVID-19 pandemic on children is yet unknown.

Shreya Gupta, MD

Institute of Pediatrics

Max Smart Super Speciality Hospital

New Delhi, India

Nipun Malhotra, MD

Department of Pulmonary

Critical Care and Sleep Medicine

Table. Epidemiologic differences in 3 coronavirus diseases (SARS, MERS, and COVID-19) and H1N1-influenza pandemic (2009)

Epidemiologic factor	SARS ^{4,7,8}	MERS ⁴	H1N1 pandemic 2009 ^{2,9-14}	COVID-19 ^{3,6,15-17}
Percentage of positive cases that were children (0-18 y)	<5%	0.1%-4%	73% (0-24 y)	PRC: 2.4% ITA: 1.2% US: 5%
Percentage of positive cases that were children (0-9 y)	SDN	SDN	13% (0-4 y)	PRC: 1% ITA: 0.5% US: SDN
Percentage of patients with severe or critical illness children	5%	SDN	SDN	PRC: 2.7% ITA: SDN US: 2%
Percentage of children requiring mechanical ventilation	<1%	<1%	SDN	PRC: <1% ITA: <1% US: <1%
Percentage children among hospitalized individuals	SDN	SDN	40%	PRC: 10% ITA: <0.1% US: <1%
Mortality rate in children	<1%	6%	0.002%-0.013%	PRC: <0.1% ITA: <0.1% US: <0.1%
Mortality rate in ICU admissions children	SDN	SDN	6.3%-11.6%	PRC: <0.1% ITA: <1% US: <0.1%

ICU, intensive care unit; ITA, Italy; MERS, Middle East respiratory syndrome; PRC, China; SARS, severe acute respiratory syndrome; SDN, sufficient data are not available.

VMMC and Safdarjung Hospital
New Delhi, India

Nitesh Gupta, DM

Department of Pulmonary
Critical Care and Sleep Medicine
VMMC and Safdarjung Hospital
New Delhi, India

Sumita Agrawal, DM

Department of Pulmonary Medicine
Medipulse Hospital
Jodhpur, Rajasthan, India

Pranav Ish, DM

Department of Pulmonary
Critical Care and Sleep Medicine
VMMC and Safdarjung Hospital
New Delhi, India

<https://doi.org/10.1016/j.jpeds.2020.04.062>

References

- Who is at High Risk for Flu Complications? Centers for Disease Control and Prevention (CDC, USA). <https://www.cdc.gov/flu/highrisk/index.htm>. Accessed April 6, 2020.
- Jhung MA, Swerdlow D, Olsen SJ, Jernigan D, Biggerstaff M, Kamimoto L, et al. Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. *Clin Infect Dis* 2011;52(suppl 1):S13-26.
- Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* 2020. <https://doi.org/10.1111/apa.15270> [Epub ahead of print].
- Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19. An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J* 2020;39:355-68.
- Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020. <https://doi.org/10.1542/peds.2020-0702> [Epub ahead of print].
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.
- Principi N, Bosis S, Esposito S. Effects of coronavirus infections in children. *Emerg Infect Dis* 2010;16:183-8.
- Lau AC-W, Yam LY-C, So LK-Y. Management of critically ill patients with severe acute respiratory syndrome (SARS). *Int J Med Sci* 2004;1:1-10.
- World Health Organization. Epidemiological summary of pandemic influenza A (H1N1) 2009 virus – Ontario, Canada, June 2009. Weekly epidemiological record. 20 November 2009. No. 47, 84. p. 485-92. Available at: <https://www.who.int/wer/2009/wer8447.pdf>. Accessed April 6, 2020.
- Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009. *N Engl J Med* 2009;361:1935-44.
- Skarbinski J, Jain S, Bramley A, Lee EJ, Huang J, Kirschke D, et al. Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States—September–October 2009. *Clin Infect Dis* 2011;52(suppl 1):S50-9.
- Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010;362:1708-19.
- Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis* 2012;12:687-95.
- Louie JK, Jean C, Acosta M, Samuel MC, Matyas BT, Schechter R. A review of adult mortality due to 2009 pandemic (H1N1) influenza A in California. *PLoS One* 2011;6:e18221.
- Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). World Health Organization (WHO). <https://www.who.int/docs/default-source/coronavirus/who-china-joint-mission-on-covid-19-final-report.pdf>. Accessed April 6, 2020.
- Sorbello M, El-Boghdady K, Di Giacinto I, Cataldo R, Esposito C, Falchetta S, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia* 2020. <https://doi.org/10.1111/anae.15049> [Epub ahead of print].
- CDC COVID-19 Response Team. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19)—United States, February 12–March 16, 2020. <https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6912e2-H.pdf>. Accessed April 6, 2020.

Severe neutropenia in infants with severe acute respiratory syndrome caused by the novel coronavirus 2019 infection



To the Editor:

Infection with severe acute respiratory syndrome caused by the novel coronavirus 2019 (SARS-CoV-2) and resulting coronavirus disease 2019 (COVID-19) is a global pandemic.¹ Pediatric cases have some peculiarities, such as milder clinical manifestations and different laboratory abnormalities.² A systematic review on laboratory data identified 12 articles, with a total of 66 pediatric patients.³⁻¹⁵ Lymphopenia was found in only 3% of children, whereas lymphopenia often is described in adult patients.^{16,17} Neutropenia was recorded in 6% of cases, but it was never less than $0.500 \times 10^9/L$ in this population.³

We describe a 23-day-old and a 39-day-old infant with mild COVID-19 and severe neutropenia who were cared for at our tertiary care referral pediatric hospital. They both came to medical attention with low-grade fever and mild respiratory symptoms with a history of contact with an infected person or persons. At admission, leukocyte and neutrophil counts were normal, nasopharyngeal swab tested positive for COVID-19, and co-infection with influenza-like viruses was excluded. On the fifth day and days after the beginning of symptoms, the 39-day-old girl and the 23-day-old girl developed severe neutropenia, with a nadir of $0.244 \times 10^9/L$ neutrophils and $0.482 \times 10^9/L$ neutrophils, respectively (Figure). No other alterations on routine examinations were recorded and the neutrophil values improved without clinical complications.

The presence of isolated severe neutropenia has not been described in children with COVID-19. This finding is noteworthy, because postinfectious transient neutropenia has been associated with many other viral infections in infancy, which might share pathogenic mechanisms.^{18,19} Moreover, the evidence of neutropenia in neonates and infants could be another manifestation