

Epidemiological and clinical features of Croatian children and adolescents with a PCR-confirmed coronavirus disease 2019: differences between the first and second epidemic wave

Krajcar, Nina; Stemberger Marić, Lorna; Šurina, Anja; Kurečić Filipović, Sanja; Trkulja, Vladimir; Roglić, Srđan; Tešović, Goran

Source / Izvornik: *Croatian Medical Journal*, 2020, 61, 491 - 500

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.3325/cmj.2020.61.491>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:177121>

Rights / Prava: [Attribution-NonCommercial-NoDerivatives 4.0 International/Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2025-01-20**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



Croat Med J. 2020;61:491-500

<https://doi.org/10.3325/cmj.2020.61.491>

Epidemiological and clinical features of Croatian children and adolescents with a PCR-confirmed coronavirus disease 2019: differences between the first and second epidemic wave

Aim To describe epidemiological and clinical features of Croatian children and adolescents with a polymerase chain reaction (PCR)-confirmed coronavirus disease 2019.

Methods Data on patients aged ≤ 19 years with a positive SARS-CoV-2 PCR test recorded in the period March 12-May 12 (first wave) and June 19-July 19, 2020 (second wave) were retrospectively analyzed. The periods were separated by several weeks with no incident cases.

Results We analyzed data on 289 children and adolescents (6.5% of all cases; incidence rate [IR] = 3.54, 95% confidence interval [CI] 3.14-3.97/million person-days), 124 in the first wave (IR = 2.27) and 165 in the second wave (IR = 6.37): IRR second/first = 2.71 (2.13-3.44). During the first wave, the incidence was highest in infants (IR = 3.48), while during the second wave it progressively increased to IR = 7.37 in 15-19-year olds. Family members were the key epidemiological contacts (72.6% cases), particularly during the first wave (95.8% vs 56.3%). Overall, 41.3% patients were asymptomatic, 25.3% in the first and 52.6% in the second wave. Age 15-19 years (vs younger) was associated with a higher (RR = 1.26, 1.02-1.54) and infection in the second wave with a lower probability (RR = 0.66, 0.53-0.81) of being symptomatic. The most common symptoms were fever, cough, and rhinorrhea. In children aged ≥ 7 years, headache, anosmia/ageusia, and sore throat were also recorded. Only one child suffered a severe disease. All but 18 (7.8%) children were treated only symptomatically, and all fully recovered.

Conclusion A large proportion of SARS-CoV-2 PCR-positive children/adolescents were asymptomatic. The associated disease was predominantly mild, comparably so in the first and second pandemic wave.

Nina Krajcar¹, Lorna Stemberger Marić^{1,2}, Anja Šurina¹, Sanja Kurečić Filipović³, Vladimir Trkulja⁴, Srđan Roglić¹, Goran Tešović^{1,5}

¹Pediatric Infectious Diseases Department, University Hospital for Infectious Diseases "Dr. Fran Mihaljević," Zagreb, Croatia

²University of Zagreb, School of Dental Medicine, Zagreb, Croatia

³Croatian Institute for Public Health, Zagreb, Croatia

⁴Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia

⁵University of Zagreb School of Medicine, Zagreb, Croatia

Received: October 12, 2020

Accepted: November 29, 2020

Correspondence to:

Nina Krajcar
Pediatric Infectious Diseases
Department
University Hospital for Infectious
Diseases "Dr. Fran Mihaljević"
Mirogojska 8
10000 Zagreb, Croatia
ninakrajcar@gmail.com

Since the late December 2019, coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread quickly worldwide and as of early December accounts for more than 65 million cases diagnosed in more than 200 countries (1). At this point, the most affected countries in Europe are Russia, Spain, France, United Kingdom (UK), and Italy with consequently the highest mortality rates. The first case in Croatia was reported in the late February 2020, and within the next two months the infection expanded nationwide. During this first epidemic wave, Croatia was under a one-month lockdown, which rapidly decreased the disease incidence, and only a few newly diagnosed cases were reported between May 25 and June 18, 2020. Easing of restrictions increased the incidence in late June, causing a second wave of COVID-19 in Croatia, with >147 000 cases reported so far (1,2).

Over the last two decades, there were two other coronavirus outbreaks. Severe acute respiratory syndrome coronavirus appeared in 2002, affecting around 8000 people, with 10% mortality. Children (4 months-17 years) accounted for <0.02% of total cases, and there was no reported death in this age group. During the outbreak of the Middle East respiratory syndrome coronavirus, around 2300 people were infected, and children (<19 years of age) were rarely affected as well (2% of total cases; 2 reported deaths) (3,4). COVID-19 has exhibited a similar epidemiological pattern. Although early reports from China, Italy, and the United States (US) suggested that children and adolescents accounted for only 1%-2% of the overall COVID-19 cases (5-7), later reports around the world indicated a higher proportions of pediatric cases, between 1%-8% (8-10). Children of all ages can be affected by SARS-CoV-2 infection, but in contrast to other respiratory viruses, they usually suffer a mild or asymptomatic infection. Compared with adults, severe infections and fatal outcomes in children are rare, and several immunopathological mechanisms could be responsible for such differences in disease severity (11). Although many studies have reviewed the features of adults with COVID-19, overall data regarding pediatric cases are scarce, and most of them are reports from China and the US, with only a few studies describing disease in children from European countries.

We aimed to describe epidemiological and clinical features of children and adolescents with COVID-19 confirmed by the polymerase chain reaction (PCR) test for SARS-CoV-2 in Croatia and to assess potential dif-

ferences between the first (March-May 2020) and second (on-going) pandemic wave (June-July 2020).

PATIENTS AND METHODS

In this retrospective analysis, eligible for inclusion were children and adolescents (0-19 years old) from the entire Croatia in whom a positive real-time PCR (RT-PCR) test for SARS-CoV-2 in nasopharyngeal/oropharyngeal swab samples was recorded between March 12, 2020 (the first positive PCR test result in a child in Croatia) and May 12, 2020 (the last positive PCR test result in a child during the first pandemic wave), and between June 19 (the first positive PCR test result in a child after several weeks) and July 19, 2020 (the second and still on-going pandemic wave). These two periods were separated by several weeks with virtually no incident cases. The samples were collected and processed in regional hospitals and Public Health Departments across the country. During the first wave, testing was recommended for persons with: 1) respiratory symptoms without alternate etiology and positive epidemiological criteria (travel to areas with local COVID-19 transmission/close contact with a confirmed or possible COVID-19 case within 14 days); 2) severe acute respiratory infection that cannot be explained by another etiology. Indications for testing during June/July were more extensive and referred to other, non-respiratory symptoms (eg, diarrhea/vomiting, headache), and the epidemiological criteria did not have to be present if the symptoms were COVID-19 compatible. The children were initially identified through the Croatian National Infectious Diseases Registry. Data from all patients treated in the main Croatian regional hospitals (Zagreb, Rijeka, Split, Osijek, Pula) were included. Epidemiological and clinical particulars were extracted from hospital medical records or, where appropriate, through direct contacts with the parents/guardians or adolescents (≥ 16 years of age) who had signed an informed consent. This study was approved by the Ethics Committees of the University Hospital for Infectious Diseases "Dr. Fran Mihaljević" and the Croatian Institute of Public Health.

Statistical analysis

All recorded cases were used to calculate overall and age-specific incidence rates (IR) using the 2011 Croatian census data for age groups 0-19 years. Incidence rate ratios (IRR second/first wave) were used to compare the incidence rates between two pandemic waves. Epidemiological and clinical characteristics are summarized overall and by pandemic wave. Patients were classified in respect to

disease severity according to the WHO criteria (12). To assess the potential association between age and pandemic wave and the probability of having a symptomatic disease, log-binomial models were fitted to the proportion of symptomatic children. We fitted frequentist (SAS 9.4 for Windows, Cary, NC, USA) and also more conservative Bayesian models (weakly informative conservative normal priors [0, 2.5, scaled to coefficients]) using rstanarm package in R (13).

RESULTS

A total of 289 children/adolescents ≤ 19 years of age with a PCR-confirmed COVID-19 (6.5% of all observed COVID-19 cases in Croatia) were recorded (Figure 1): 124 during the first (5.7% of all cases during this period) and 165 during the second pandemic wave (7.3% of all cases). The overall incidence rate was 3.54 cases/million person-days, and was 2.7 times higher during the second wave (IRR=2.71, 95%CI 2.13-3.44) (Table 1). Crude rates were practically identical to the rates age-standardized to the Standard European Population (Table 1). Overall IRs were similar across age groups (Table 1), but during the first wave IR was the highest in infants, while in the second wave it progressively increased to 7.37/million person-days in 15-19-year-olds (Table 1). Of the 289 recorded children, data on 59 (20.4%) were not available for a more detailed evaluation (Figure 1): they were not hospitalized before or within 30 days after the PCR testing, and their medical histories could not be traced. Although with some uncertainty, it is reasonable to conclude that they suffered only mild symptoms, if any at

all. Considering the remaining 230 patients, family members were the main source of infection (72.6%), more so in the first wave (95.8%) than in the second wave (56.3%) (Table 2). Other likely sources of infection were social gatherings, preschools/daycare centers, and after-school activities (1/95 children in the first period vs 30.4% in the second) (Table 2). The affected children were otherwise healthy, with 16.1% suffering from pre-existing conditions, mostly asthma and recurrent bronchial spasms or pneumonia (Table 2). Apart from one newborn, all had a history of Bacillus Calmette-Guérin (BCG) vaccination. A considerable proportion of children (41.3% overall, 25.3% and 52.6% in the first and the second wave, respectively) had no symptoms before and up to four weeks after testing, hence were considered asymptomatic (Table 3). The most common symptoms were fever (body temperature >37 °C) (47.0%), which was usually low-grade (the median peak fever was 38 °C and median duration was 2 days), cough (16.5%), and runny nose (11.3%) (Table 3). Gastro-intestinal symptoms were rare (Table 3), and only 6 patients (2.6%) where tachypneic or dyspneic at a particular point in time and 5 suffered conjunctivitis (2.2%) (Table 3). Skin changes were present in only 2 patients: urticaria and maculopapular rash. Febrile seizures were reported in one, previously healthy, toddler, while all the other children did not have any symptom of central nervous system involvement.

In children ≥ 7 years of age, headache (19.2%), anosmia/ageusia (17.9%), and sore throat (11.3%) were also observed (Table 3). Symptomatic children experienced almost exclusively a mild disease (133/135) (Table 3). Only

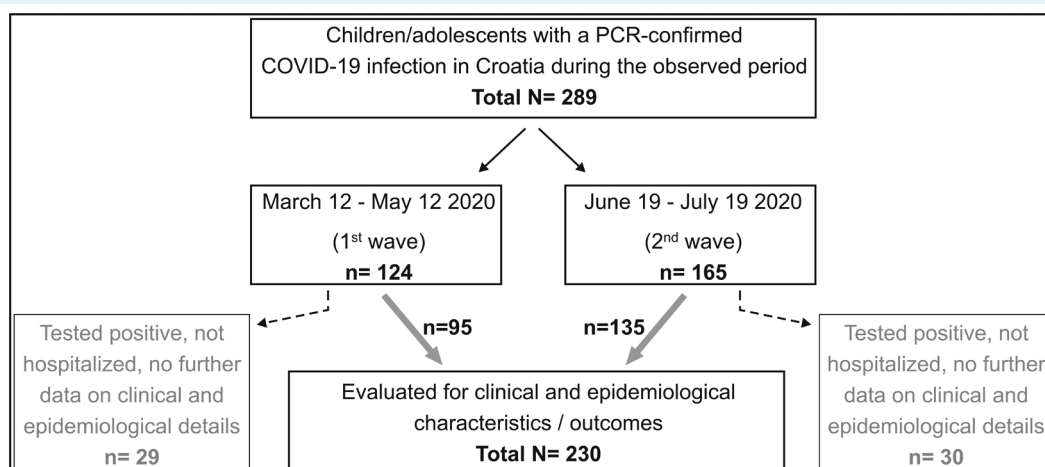


FIGURE 1. Study outline.

2 children were hospitalized for medical reasons (Table 2), one of whom suffered pneumonia ("moderate disease") and the other severe pneumonia: a 16-year old girl with obesity and a history of behavioral disorder was admitted to the ICU and was treated with oxygen therapy, supportive measures, anticoagulants, dexamethasone, and antibiotics (azithromycin and ceftriaxone) for suspected bacterial coinfection. There were no cases of confirmed bacterial coinfection, sepsis, acute respiratory distress syndrome, or

multisystem inflammatory syndrome in children. Only 18 children (7.8%) received treatments other than symptomatic, and all fully recovered (Table 3).

There was a trend of higher probability of being symptomatic with older age, regardless of the pre-existing comorbidity (Table 4). With further adjustment for the observed period, the probability of being symptomatic was higher in 15-19-year-olds than in younger age groups (RR= 1.26,

TABLE 1. Incidence rates (IR/1 000 000 person days of observation) of children/adolescents (age 0-19 years) with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 virus during the first (March 12-May 12) and second wave (June 19-July 19) of coronavirus disease-19 pandemic in Croatia. All estimates are presented with 95% confidence intervals

	Total	First wave	Second wave	Incidence rate ratio second/first
Observed period, days	91	61	30	—
Number with +PCR	289	124	165	—
Crude IR	3.54 (3.15-3.97)	2.27 (1.88-2.70)	6.13 (5.23-7.14)	2.71 (2.13-3.44)
Crude by age in years (n, IR)				
Up to 1	15, 3.89 (2.18-6.41)	9, 3.48 (1.59-6.61)	6, 4.72 (1.73-10.3)	1.36 (0.40-4.26)
1 to 4	50, 3.22 (2.39-4.25)	22, 2.12 (1.33-3.21)	28, 5.48 (3.64-7.92)	2.59 (1.43-4.75)
5 to 9	66, 3.55 (2.74-4.52)	27, 2.17 (1.43-3.15)	39, 6.36 (4.52-8.70)	2.94 (1.75-4.99)
10 to 14	67, 3.13 (2.42-3.97)	29, 2.02 (1.35-2.90)	38, 5.38 (3.81-7.38)	2.66 (1.60-4.48)
15 to 19	91, 4.10 (3.30-5.03)	37, 2.48 (1.75-3.42)	54, 7.37 (5.54-9.62)	2.97 (1.92-4.64)
Standardized IR EU*	3.53 (3.13-3.97)	2.26 (1.88-2.70)	6.13 (5.23-7.15)	—

*Age-standardization to Standard European Population (EU-27 plus EFTA 2011-2030 population) (<https://seer.cancer.gov/stdpopulations/world.who.html>), accessed October 3, 2020)

TABLE 2. Epidemiological characteristics of children with a positive polymerase chain reaction (PCR) test for SARS-COV-2 during the first (March 12-May 12) and second (June 19-July 19) pandemic wave in Croatia. Data are count (%) if not otherwise stated

	Total	First wave	Second wave
N	230	95	135
Girls	131 (56.9)	54 (56.8)	77 (57.0)
Age in years (median, interquartile range, range)	10.0 (4.6-15.7; 0.02-19)	8.1 (3.2-15.4; 0.2-19.0)	11.8 (6.3-15.8; 0.02-18.9)
up to 1	14 (6.1)	9 (9.5)	5 (3.7)
1-4	44 (19.1)	21 (22.1)	23 (17.0)
5-9	54 (23.5)	22 (23.2)	32 (23.7)
10-14	51 (22.2)	19 (20.0)	32 (23.7)
15-19	67 (29.1)	24 (25.3)	43 (31.9)
Imported infection	11 (4.8)	9 (9.5)	2 (1.5)
Infection source: family/other/unknown	167 (72.6)/42 (18.3)/21 (9.1)	91 (95.8)/1/3	76 (56.3)/41 (30.4)/18 (13.3)
First symptomatic person			
family members	165 (71.7)	87 (91.6)	78 (57.8)
friends/other contacts	8 (3.5)	2 (2.1)	6 (4.4)
child (patient)	34 (14.8)	1 (1.0)	33 (24.4)
unknown	23 (10.0)	5 (5.3)	18 (13.3)
Children with comorbidities	37 (16.1)	21 (22.1)	16 (11.8)
asthma/recurrent spasms/pneumonia	14	7	7
allergic rhinitis/recurrent otitis media	6	4	2
rheumatologic diseases	4	2	2
any other	13	8	5

1.02-1.54) and lower in children affected in the second wave (RR=0.66, 0.53-0.81) (Table 5).

Testing (negative findings) for SARS-CoV-2 was repeated in 93/230 (40.4%) children (61.1% vs 25.9% in the first and second wave, respectively), with a time lag ranging between 4 and 63 days.

DISCUSSION

The present data are in line with reports from other countries suggesting that children and adolescents represent

only a small proportion of COVID-19 patients. The median age in the present study was higher than reported in studies from Italy (3.3 years) and UK (4.6 years) but similar to that reported in China (6-7 years) and North America (11 years) (14-17). The present study is specific in that we collected nationwide data through a network of Public Health Departments and hospitals designated for monitoring of the pandemic and patient treatment. The epidemiological network consists of 21 regional Public Health Departments (in 21 administrative units, Counties), with rather extensive testing whenever indicated by epidemiological circumstances. As a consequence of broad testing, the estimated

TABLE 3. Clinical characteristics of children with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 during the first (March 12-May 12) and second (June 19-July 19) pandemic wave in Croatia. Data are count (%) if not otherwise stated

	Total (N=230)	First wave (n=95)	Second wave (n=135)
No symptoms/any symptoms	95 (41.3)/135 (58.7)	24 (25.3)/71 (74.7)	71 (52.6)/64 (47.4)
Fever/duration (days; median, range)	108 (47.0)/2 (1-14)	63 (66.3)/2 (1-14)	45 (33.3)/2 (1-8)
Peak fever (°C; median, range)	38.0 (37.2-40.0)	38.0 (37.2-40)	38.0 (37.2-39.8)
Cough	38 (16.5)	22 (23.2)	16 (11.9)
Runny nose	26 (11.3)	14 (14.7)	12 (8.9)
General infective syndrome	26 (11.3)	23 (24.2)	3 (2.2)
Vomiting	8 (3.5)	5 (5.3)	3 (2.2)
Diarrhea	7 (3.0)	4 (4.2)	3 (2.2)
Tachypnea/dyspnea	6 (2.6)	5 (5.3)	1 (0.7)
Conjunctivitis	5 (2.2)	1 (1.0)	4 (3.0)
Skin changes	2 (0.8)	1 (1.0) (urticarial)	1 (0.7) (maculopapular)
Febrile convulsions	1 (0.4)	1 (1.0)	0
Laryngitis	1 (0.4)	1 (1.0)	0
Considering children ≥7 years of age			
headache	29/151 (19.2)	15/52 (28.8)	14/95 (14.7)
anosmia/ageusia	27/151 (17.9)	13/52 (25.0)	14/95 (14.7)
sore throat	17/151 (11.3)	10/52 (19.2)	7/95 (7.4)
chest or abdominal pain	7/151 (4.6)	5/52 (9.6)	2/95 (2.1)
x-ray normal/not done/pneumonia	1/227 (98.7)/2	1 (1.1)/94 (98.9)/0	0/133 (98.5)/2 (1.5)
Hospitalized due to disease severity	2 (6 days, 11 days)	0	2 (6 days, 11 days)
Hospitalized-epidemiological reasons	9 (3.9) (7-21 days)	8 (7-21 days)	1 (9 days)
Disease severity WHO criteria			
mild disease	133/135 symptomatic	71/71 symptomatic	62/64 symptomatic
pneumonia	1	0	1/64 symptomatic
severe pneumonia	1	0	1/64 symptomatic
acute respiratory distress syndrome, sepsis, septic shock	0	0	0
Treatment apart from symptomatic	18 (7.8)	11 (11.6)	7 (5.2)
Azithromycin	8	2	6
Inhaled anti-asthmatics	4	2	2
Systemic corticosteroids	2	1	1
Inhaled epinephrine	1	1	0
Oseltamivir	1	1	0
LMWH	1	0	1
Penicillins/cephalosporins	8	6	2
Complications/sequels	0	0	0

TABLE 4. Distribution of children with “any symptom” across age groups and in respect to comorbidity. Data are n/N (%)

Age, years	Comorbidity			Total
	none	respiratory/rheumatic	any other	
Up to 1	8/13 (61.5)	—	1/1 (100)	9/14 (64.3)
1-4	24/37 (64.9)	2/4 (50.0)	0/3 (0)	26/44 (59.1)
5-9	18/42 (42.9)	4/8 (50.0)	2/4 (50.0)	24/54 (44.4)
10-14	25/46 (54.4)	4/5 (80.0)	—	29/51 (56.9)
15-19	36/55 (64.5)	6/7 (85.7)	5/5 (100)	47/67 (70.1)
Total	111/193 (57.5)	16/24 (66.6)	8/13 (61.5)	135/230 (58.7)

TABLE 5. Summary of multivariate analysis of probability of being symptomatic*

	Frequentist		Bayesian		
	RR (95%CI)	P	RR (95%CrI)	probabilities	BF
Age 15-19 vs younger	1.26 (1.02-1.54)	0.030	1.21 (1.00-1.48)	P(RR)>1.0=97.2%	7.7
Second wave	0.66 (0.53-0.81)	<0.001	0.66 (0.53-0.82)	P(RR)<1.0=99.9%	16.6
Any comorbidity	1.19 (0.88-1.61)	0.249	1.02 (0.86-1.15)	P(RR)>1.0=61.6%	0.019

*RR – risk ratio; BF – Bayes factor; CrI – credible interval.

incidence rates could be reasonably close to the actual situation, although the important question regarding the number of incident cases (eg, asymptomatic) that were missed remains unanswered. The incidence rates suggest that in the overall observed period children/adolescents of different age were similarly affected. However, there appeared several considerable differences between the two periods: a) in the first wave the IRS were highest in newborns when compared with other age groups; b) in the second wave there was a clearly higher incidence overall and in each age group; c) in the second wave the incidence increased with older age. In part, the discrepancies are likely due to the fact that the first wave included a one-month period of a complete lockdown (closing of preschools/schools/universities/public transport, restrictions on public gatherings, international and intra- country travel, closing of all-but-essential workplaces, case isolation and home quarantine for close contacts, comprehensive contact tracing), followed by virtually no incident cases between May 25 and June 18, 2020, which led to gradual easing of restrictions. The second wave (June 19-July 19), on the other hand, was characterized by considerably relaxed epidemiological measures (reopening of preschools/workplaces, easing restrictions on public gatherings and travel, but case isolation, home quarantine for close contacts, and comprehensive contact tracing remained the same). Another possible source of the differences might be the fact that in the second wave more extensive PCR testing was undertaken (ie, broader epidemiological indications). The rise in incident cases and the observed difference in age-specific rates coincides also with the differences in the most likely transmission

settings: in the first wave practically all patients acquired the infection from their family members (no cases of health care-acquired infections), while in the second wave a considerable proportion of children acquired SARS-CoV-2 outside of home (possibly from other adults or children in preschools and daycares). The role of children and adolescents in the context of household and community transmission is currently in the focus of intense discussions because it impacts social and economic issues and affects the reopening of schools. A European multicenter study conducted during the initial peak of COVID-19 pandemic showed that the most common source of infection in children was a parent or a sibling (60%) (14). Another study suggested that children mainly acquired the infection from an adult contact, and that secondary transmission from children was low (18). Only a few case reports have suggested transmission from children to other family members and, a relationship between school closures and transmission dynamics has not been conclusively proven (19-22).

It has been suggested that the viral spread could be affected by SARS-CoV-2 mutations. Currently, the globally predominant strain is the D614G variant, which has replaced the D614 strain (the Wuhan strain), the dominant strain in the early stage of the pandemic (23). The transformation from D614 to D614G started in Europe during March. D614G then spread to North America and the rest of the world, accounting for 78% of global sequences by the end of May 2020. While D614G results in a higher viral load and is more contagious than D614, currently there is no evidence that the infection with this variant would result in a more severe dis-

ease (23-25). Croatia has obtained whole-genome sequences for only a small number of SARS-CoV-2 isolates from patients during March and April 2020 and deposited them in GISAID (the main SARS-CoV-2 genomes open-source database). Only one strain contained the D614G variant (26,27). It was detected in a sample collected in Dubrovnik-Neretva County in late March, while other strains from different Croatian counties did not contain this mutation. Generally, the number of the presented cases, overall and by the observed period, is relatively limited, which precluded any meaningful comparisons across Croatian counties, which largely differ in population: most contributed just a few or no cases, overall or by the observed period. In the first wave, IR (age-adjusted to Croatian population) in the Dubrovnik-Neretva County was 4.18 (1.68-8.65) cases/million person-days, and it was 1.23 (0.03-6.91) in the second period. However, there were only 7 cases in the first and one case in the second period – hence, the estimated difference between the two rates (IRR=3.40, 95%CI 0.46-141) is extremely imprecise, and data do not provide a basis for any assumptions about the relevance of the isolated D614G strain.

A large proportion of PCR-positive children/adolescents were asymptomatic: 41.3% overall, 25.3% in the first and 52.6% in the second wave, and there appeared a mild but clear trend of higher probability of being symptomatic with older age. This prevalence of asymptomatic children is considerably higher than reported in different European countries, China, Republic of Korea, Iran, and the US (in the range between 4.0% and 28.0%) (14,28-34). In this respect, the following should be noted: a) we adhered to the WHO and the European Centre for Disease Prevention and Control definition of a “COVID-19 patient” as a subject with a positive PCR test regardless of the presence of symptoms; b) the present proportions might not be exactly correct, since 59/289 of the recorded PCR-positive subjects could not have been reliably evaluated for the presence of symptoms. However, even if symptomatic, they most likely suffered a mild(er) disease and were not hospitalized; c) the designation of “asymptomatic” was based on the evaluation over a period that extended from around 7 days before the PCR test to 30 days after testing (so, no misclassification was likely); d) most of the published reports were focused on hospitalized children or those who were admitted to hospital at least transiently, while the present results pertain to children/adolescents who were tested even when considered a relatively remote contacts of other “positive” or symptomatic people. The latter notion could induce speculation about the actual positive predictive values of different PCR tests (ie, specificity in clinical settings), rele-

vance of the viral load, and other topics that are far beyond the scope of the present work.

Practically all symptomatic children (133/135) experienced a mild disease – fever and respiratory tract infection symptoms without pneumonia, which is discordant with the suggested (higher) proportion of children with a moderate (39%) disease in a recent systematic review embracing 1475 children (32). The proportions of children with severe (2%) and critical illness (0.7%) were comparable with those in our study. The present data are also in disagreement with the suggested higher probability of a severe disease in infants (<12 months of age) (14,35-42). Furthermore, gastrointestinal symptoms were less common in the present study as compared with other reports (5%-7% or 10%-35%) (14-16,43). In a way, this is in agreement with the suggested higher prevalence of gastrointestinal symptoms in children with a more severe COVID-19 (44).

A number of hypotheses have been proposed to explain the usually mild or asymptomatic SARS-CoV-2 infection in children and young people. Possible reasons include the presence of cross-reactive antibodies due to frequent contacts with seasonal coronaviruses, different expression of angiotensin-converting enzyme 2 across age groups, recent vaccinations (BCG) that produce broad protection against viral infection and sepsis, and more active innate immune response compared with adults (45). BCG vaccination has been suggested to be associated with reduced COVID-19 morbidity and mortality (46-48). Croatia has been implementing universal BCG vaccination since 1948 and has high BCG immunization coverage, which could attenuate the severity of COVID-19 in our citizens, especially among children, who are the most recently vaccinated population. However, the discrepancy between the proportions of asymptomatic children/adolescents in the first and the second wave is difficult to explain. Apart from the more extensive testing during the second wave, no other potential explanation seems reasonable. Although it has been anecdotally (but without any sound data) suggested that with higher ambient temperature the clinical presentation of COVID-19 could be milder, the present data provide no grounds for speculations of this kind: the two observed periods were characterized by substantially different epidemiological circumstances. Further studies on viral loads could possibly explain a lower incidence during hot periods of the year.

The present analysis is limited by a relatively small sample and a lack of detailed epidemiological and clinical data for 59/289 PCR-positive participants. They were

not hospitalized in regional hospitals, and we were unable to establish a direct contact with consenting parents/caregivers or primary care physicians. It seems reasonable to assume it unlikely that any clinically relevant form of the disease remained unreported/unrecorded – hence, they probably suffered only mild symptoms or were asymptomatic.

In conclusion, the present data suggest that COVID-19 in Croatian children and adolescents results in a mild and often asymptomatic disease. Critical disease forms and deaths in this age group in our population have not been reported yet.

Funding None.

Ethical approval given by the Ethics Committees of the University Hospital for Infectious Diseases “Dr. Fran Mihaljević”, Zagreb, Croatia (01-1045-9-2020), and the Croatian Institute of Public Health (381-15-20-2).

Declaration of authorship NK, LSM, SR, and GT conceived and designed the study; NK, LSM, AŠ, and SKF acquired the data; NK and VT analyzed and interpreted the data; NK, AŠ, VT, SR, and GT drafted the manuscript; NK, LSM, SKF, VT, SR, and GT critically revised the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

- WHO. Coronavirus disease (COVID-19) Dashboard. Available from: https://covid19.who.int/?gclid=CjwKCAjw_Y_8BRBiEiwA5MCBjQqC1cyWprfH3ktRHSAsrWX3LchTDChdo5G3c7tsKjjZ4epZUkFX8BoCl6AQAvD_BwE. Accessed: December 6, 2020.
- ECDC. Weekly surveillance report on COVID-19. Week 48, 2020. Available from: https://covid19-country-overviews.ecdc.europa.eu/#7_croatia. Accessed: December 6, 2020.
- She J, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol*. 2020;92:747-54. [Medline:32232980](https://pubmed.ncbi.nlm.nih.gov/32232980/) [doi:10.1002/jmv.25807](https://doi.org/10.1002/jmv.25807)
- Graham RL, Baric RS. Recombination, reservoirs, and the modular spike: mechanisms of coronavirus cross-species transmission. *J Virol*. 2010;84:3134-46. [Medline:19906932](https://pubmed.ncbi.nlm.nih.gov/19906932/) [doi:10.1128/JVI.01394-09](https://doi.org/10.1128/JVI.01394-09)
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-42. [Medline:32091533](https://pubmed.ncbi.nlm.nih.gov/32091533/) [doi:10.1001/jama.2020.2648](https://doi.org/10.1001/jama.2020.2648)
- Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020;323:1335. [Medline:32181795](https://pubmed.ncbi.nlm.nih.gov/32181795/) [doi:10.1001/jama.2020.4344](https://doi.org/10.1001/jama.2020.4344)
- COVID-19 Clinical Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:422-6. [Medline:32271728](https://pubmed.ncbi.nlm.nih.gov/32271728/) [doi:10.15585/mmwr.mm6914e4](https://doi.org/10.15585/mmwr.mm6914e4)
- Age distribution of coronavirus (COVID-19) cases in South Korea as of August 21, 2020. Available from: <https://www.statista.com/statistics/1102730/south-korea-coronavirus-cases-by-age/>. Accessed: August 25, 2020.
- Posfay-Barbe KM, Wagner N, Gauthey M, Moussaoui D, Loevy N, Diana A, et al. COVID-19 in children and the dynamics of infection in families. *Pediatrics*. 2020;146:e20201576. [Medline:32457213](https://pubmed.ncbi.nlm.nih.gov/32457213/) [doi:10.1542/peds.2020-1576](https://doi.org/10.1542/peds.2020-1576)
- Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985. [Medline:32444460](https://pubmed.ncbi.nlm.nih.gov/32444460/) [doi:10.1136/bmj.m1985](https://doi.org/10.1136/bmj.m1985)
- Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109:1088-95. [Medline:32202343](https://pubmed.ncbi.nlm.nih.gov/32202343/) [doi:10.1111/apa.15270](https://doi.org/10.1111/apa.15270)
- WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. – Interim guidance, 13 March 2020. Available from: https://apps.who.int/iris/handle/10665/331446?search-result=true&query=10665%2F331446&scope=&rpp=10&sort_by=score&order=desc. Accessed: December 2, 2020.
- Goodrich G, Gabry J, Ali I, Brilleman S. rstanarm: Bayesian applied regression modeling via Stan. R package versions 2.21.1. Available from: <https://mc-stan.org/rstanarm>. Accessed: December 2, 2020.
- Gotzinger F, Santiago-Garcia B, Noguera-Julian A, Lanaspá M, Lancellata L, Calò Carducci F, et al; Ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4:653-61. [Medline:32593339](https://pubmed.ncbi.nlm.nih.gov/32593339/) [doi:10.1016/S2352-4642\(20\)30177-2](https://doi.org/10.1016/S2352-4642(20)30177-2)
- Parri N, Lenge M, Buonsenso D. Coronavirus infection in pediatric emergency departments (CONFIDENCE) research group. Children with Covid-19 in Pediatric Emergency Departments in Italy. *N Engl J Med*. 2020;383:187-90. [Medline:32356945](https://pubmed.ncbi.nlm.nih.gov/32356945/) [doi:10.1056/NEJMc2007617](https://doi.org/10.1056/NEJMc2007617)
- Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249. [Medline:32960186](https://pubmed.ncbi.nlm.nih.gov/32960186/) [doi:10.1136/bmj.m3249](https://doi.org/10.1136/bmj.m3249)
- CDC. COVID-19 Response Team. Coronavirus Disease 2019 in children – United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:422-6. [Medline:32271728](https://pubmed.ncbi.nlm.nih.gov/32271728/) [doi:10.15585/mmwr.mm6914e4](https://doi.org/10.15585/mmwr.mm6914e4)
- Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus

- infection in hospitalized infants under 1 year of age in China. *JAMA*. 2020;323:1313-4. [Medline:32058570](#) [doi:10.1001/jama.2020.2131](#)
- 19 Cao Q, Chen YC, Chen CL, Chiu CH. SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics. *J Formos Med Assoc*. 2020;119:670-3. [Medline:32139299](#) [doi:10.1016/j.jfma.2020.02.009](#)
 - 20 Zhen-Dong Y, Gao-Jun Z, Run-Ming J, Zhi-Sheng L, Zong-Qi D, Xiong X, et al. Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: A review. *J Infect*. 2020;81:e11-5. [Medline:32360500](#) [doi:10.1016/j.jinf.2020.04.030](#)
 - 21 Viner RM, Russell SJ, Croker H, Packer J, Ward J, Stansfield C, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *Lancet Child Adolesc Health*. 2020;4:397-404. [Medline:32272089](#) [doi:10.1016/S2352-4642\(20\)30095-X](#)
 - 22 Hildenwall H, Luthander J, Rhedin S, Hertting O, Olsson-Åkefeldt S, Melén E, et al. Paediatric COVID-19 admissions in a region with open schools during the two first months of the pandemic. *Acta Paediatr*. 2020;...: Epub ahead of print. [doi:10.1111/apa.15432](#). [Medline:32567145](#)
 - 23 Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell*. 2020;182:812-27. e19. [Medline:32697968](#) [doi:10.1016/j.cell.2020.06.043](#)
 - 24 Wagner C, Roychoudhury P, Hadfield J, Hodcroft EB, Lee J, Moncla LH, et al. Comparing viral load and clinical outcomes in Washington State across D614G mutation in spike protein of SARS-CoV-2. Available from: <https://github.com/blab/ncov-D614G>. Accessed: December 2, 2020.
 - 25 Lorenzo-Redondo R, Nam HH, Roberts SC, Simons LM, Jennings LJ, Qi C, et al. A unique clade of SARS-CoV-2 viruses is associated with lower viral loads in patient upper airways. *medRxiv [Preprint]*. 2020 May 26;2020.05.19.20107144.
 - 26 Jurak I, Rukavina T, Vugrek O. Successful sequencing of the first SARS-CoV-2 genomes from Croatian patients. *Croat Med J*. 2020;61:302-3. [Medline:32643351](#) [doi:10.3325/cmj.2020.61.302](#)
 - 27 GISAID (Global Initiative on Sharing All Influenza Data). Available from: <https://www.gisaid.org/epiflu-applications/hcov-19-genomic-epidemiology/>. Accessed: December 2, 2020.
 - 28 Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. Chinese pediatric novel coronavirus study team. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382:1663-5. [Medline:32187458](#) [doi:10.1056/NEJMc2005073](#)
 - 29 CDC. COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:343-6. [Medline:32214079](#) [doi:10.15585/mmwr.mm6912e2](#)
 - 30 Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis*. 2020;20:689-96. [Medline:32220650](#) [doi:10.1016/S1473-3099\(20\)30198-5](#)
 - 31 Han MS, Choi EH, Chang SH, Jin B-L, Lee EJ, Kim BN, et al. Clinical characteristics and viral RNA detection in children with Coronavirus Disease 2019 in the Republic of Korea. *JAMA Pediatr*. 2020;...:e203988. [Medline:32857112](#) [doi:10.1001/jamapediatrics.2020.3988](#)
 - 32 Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiolo A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr*. 2020;179:1029-46. [Medline:32424745](#) [doi:10.1007/s00431-020-03684-7](#)
 - 33 Patel NA. Pediatric COVID-19: Systematic review of the literature. *Am J Otolaryngol*. 2020;41:102573. [Medline:32531620](#) [doi:10.1016/j.amjoto.2020.102573](#)
 - 34 Zhang L, Peres TG, Silva MVF, Camargos P. What we know so far about Coronavirus Disease 2019 in children: A meta-analysis of 551 laboratory-confirmed cases. *Pediatr Pulmonol*. 2020;55:2115-27. [Medline:32519809](#) [doi:10.1002/ppul.24869](#)
 - 35 Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145:e20200702. [Medline:32179660](#) [doi:10.1542/peds.2020-0702](#)
 - 36 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. [Medline:32310621](#) [doi:10.1097/INF.0000000000002660](#)
 - 37 Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. *J Pediatr*. 2020;223:14-9.e2. [Medline:32407719](#) [doi:10.1016/j.jpeds.2020.05.006](#)
 - 38 Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 disease severity risk factors for pediatric patients in Italy. *Pediatrics*. 2020;146:e2020009399. [Medline:32665373](#) [doi:10.1542/peds.2020-009399](#)
 - 39 Kainth MK, Goenka PK, Williamson KA, Fishbein JS, Subramony A, Schlein C, et al. Early experience of COVID-19 in a US children's hospital. *Pediatrics*. 2020;146:e2020003186. [Medline:32680880](#) [doi:10.1542/peds.2020-003186](#)
 - 40 Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, et al; Columbia Pediatric COVID-19 Management Group. Epidemiology, clinical features, and disease severity in patients with Coronavirus disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr*. 2020;...:e202430. [Medline:32492092](#) [doi:10.1001/jamapediatrics.2020.2430](#)
 - 41 Mithal LB, Machut KZ, Muller WJ, Kociolek LK. SARS-CoV-2

- Infection in infants less than 90 days old. *J Pediatr.* 2020;224:150. [Medline:32565095](#) [doi:10.1016/j.jpeds.2020.06.047](#)
- 42 McLaren SH, Dayan PS, Fenster DB, Ochs JB, Vindas MT, Bugaighis MN, et al. Novel Coronavirus infection in febrile infants aged 60 days and younger. *Pediatrics.* 2020;146:e20201550. [Medline:32527752](#) [doi:10.1542/peds.2020-1550](#)
- 43 CDC. COVID-19 Response Team. Coronavirus Disease 2019 in children – United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:422–6. [Medline:32271728](#) [doi:10.15585/mmwr.mm6914e4](#)
- 44 Rokkas T. Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis. *Ann Gastroenterol.* 2020;33:355–65. [Medline:32624655](#)
- 45 Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. *Clin Immunol.* 2020;220:108588. [Medline:32905851](#) [doi:10.1016/j.clim.2020.108588](#)
- 46 Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci U S A.* 2020;117:17720–6. [Medline:32647056](#) [doi:10.1073/pnas.2008410117](#)
- 47 Kinoshita M, Tanaka M. Impact of routine infant BCG vaccination on COVID-19. *J Infect.* 2020;81:625–33. [Medline:32795481](#) [doi:10.1016/j.jinf.2020.08.013](#)
- 48 Klinger D, Blass I, Rappoport N, Linial M. Significantly improved COVID-19 outcomes in countries with higher BCG vaccination coverage: A multivariable analysis. *Vaccines (Basel).* 2020;8:E378. [Medline:32664505](#) [doi:10.3390/vaccines8030378](#)