Children and Adolescents With SARS-CoV-2 Infection

Epidemiology, Clinical Course and Viral Loads

Helena C. Maltezou, MD, PhD, Ioanna Magaziotou, MD,† Xanthi Dedoukou, MD, MPH,† Eirini Eleftheriou, MD,‡ Vasilios Raftopoulos, RN, PhD,§ Athanasios Michos, MD, PhD,¶ Athanasia Lourida, MD, PhD,‖ Maria Panopoulou, MD, PhD,** Konstantinos Stamoulis, MD, PhD,†† Vasiliki Papaevangelou, MD, PhD,‡‡ Efthimia Petinaki, MD, PhD,§§ Andreas Mentis, MD, PhD,¶¶ Anna Papa, MD, PhD,‖‖ Athanasios Tsakris, MD, PhD,*** Emmanuel Roilides, MD, PhD,††† George A. Syrogiannopoulos, MD, PhD,‡‡‡ and Maria Tsolia, MD, PhD,‡ for Greek Study Group on SARS-CoV-2 Infections in Children*

Background: There is limited information on severe acute respiratory syndrome virus 2 (SARS-CoV-2) infection in children.

Methods: We retrieved data from the national database on SARS-CoV-2 infections. We studied in-family transmission. The level of viral load was categorized as high, moderate, or low based on the cycle threshold values.

Results: We studied 203 SARS-CoV-2-infected children (median age: 11 years; range: 6 days to 18.4 years); 111 (54.7%) had an asymptomatic infection. Among the 92 children (45.3%) with coronavirus disease 2019 (COVID-19), 24 (26.1%) were hospitalized. Infants <1 year were more likely to develop COVID-19 (19.5% of all COVID-19 cases) (*P*-value = 0.001). There was no significant difference between viral load and age, sex, underlying condition, fever and hospitalization, as well as between type of SARS-CoV-2 infection and age, sex, underlying condition and viral load. Transmission from a household member accounted for 132 of 178 (74.2%) children for whom the source of infection was identified. An adult member with COVID-19 was the first case in 125 (66.8%) family clusters. Child-to-adult transmission was found in one occasion only.

Conclusions: SARS-CoV-2 infection is mainly asymptomatic or mild during childhood. Adults appear to play a key role in spread of the virus in families. Most children have moderate or high viral loads regardless of age, symptoms or severity of infection. Further studies are needed to elucidate the role of children in the ongoing pandemic and particularly in light of schools reopening and the need to prioritize groups for vaccination, when COVID-19 vaccines will be available.

Key Words: SARS-CoV-2, COVID-19, children, viral load, families

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A new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in late December 2019 and subsequently spread globally, necessitating the declaration of a pandemic by the World Health Organization on March 11, 2020.[1] As of August 23, 2020, 23 million cases of the new respiratory disease named coronavirus disease (COVID-19) and 800,000 deaths have been notified globally.[1] Person-to-person transmission of SARS-CoV-2 was reported for the first time by Chan et al[2], when a family member with no history of travel to Wuhan, China became infected several days after contact with family members who returned from Wuhan. As the potential of SARS-CoV-2 unfolds, it becomes evident that asymptomatic infection and mild clinical illness are more prevalent in children than adults.[3,4] Yet, compared with adults, there are very few pediatric studies published so far.[3,4] In the context of the ongoing COVID-19 pandemic, it is important to study the epidemiologic characteristics, clinical manifestations, and transmission chains in children to guide screening, containment and preventive measures. Herein, we present the findings of the clinical and epidemiologic investigations and the viral loads of children and adolescents with SARS-CoV-2 infection in Greece.

PATIENTS AND METHODS

Surveillance and Contact Tracing of SARS-CoV-2 Infections

In Greece cases of SARS-CoV-2 infection are notified to the National Public Health Organization. Laboratory-diagnosed cases are notified daily by physicians and by laboratories testing for SARS-CoV-2 infection by real-time reverse-transcriptase polymerase chain reaction (RT-PCR). Data about hospitalized cases, admission in intensive care units (ICUs), complications, and/or COVID-19-associated deaths are also collected by the physicians in charge through telephone interviews. Contact tracing of SARS-CoV-2 infected cases is conducted and close contacts are instructed

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From the *Directorate for Research, Studies, and Documentation, National Public Health Organization, Athens, Greece; †Directorate of Epidemiological Surveillance and Interventions for Infectious Diseases, National Public Health Organization, Athens, Greece; ‡Second Department of Pediatrics, National and Kapodistrian University of Athens, Aglaia Kyriakou Children's Hospital, Athens, Greece; §Epidemiological Surveillance of HIV/AIDS Department, National Public Health Organization, Athens, Greece; ¶First Department of Pediatrics, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece; ‖Infection Prevention and Control Committee, Aghia Sofia Children's Hospital, Athens, Greece; **Laboratory of Microbiology, Democritus University of Thrace, Alexandroupolis, Greece; ††National Blood Transfusion Center, Athens, Greece; ‡‡Third Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece; §§Microbiology Laboratory, University of Thessaly, Larissa, Greece; ¶¶National Reference Laboratory for Influenza and other Respiratory Viruses, Hellenic Pasteur Institute, Athens, Greece; ‖‖Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece; ***Department of Microbiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece; †††Third Department of Pediatrics, Aristotle University School of Health Sciences, Thessaloniki, Greece; and ‡‡‡Department of Pediatrics, University of Thessaly, Larissa, Greece.

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George A. Syrogiannopoulos and Maria Tsolia contributed equally as senior authors.

Address for correspondence: Helena C. Maltezou, MD, PhD, Directorate for Research, Studies, and Documentation, National Public Health Organization, 3-5 Agrafon Street, Athens 15123, Greece. E-mail: helen-maltezou@ath.forthnet.gr.

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to stay isolated for 14 days after the last exposure. In case of onset of symptoms, contacts are advised to be tested for SARS-CoV-2. In addition, active, massive laboratory-sampling and testing by RT-PCR, regardless of symptoms, is also performed for containment purposes and in the context of investigation of clusters in closed settings or specific populations such as Roma populations or those residing in refugees' camps.

Data Collection

The study period extended from February 26 (first COVID-19 case diagnosed in Greece) to June 30, 2020. Children were identified through the national registry of SARS-CoV-2 infections. Data were collected using a standardized questionnaire per case. We contacted through telephone one parent (preferably the mother) of each child, to collect data about any other household member tested positive for SARS-CoV-2. If this was the case, information about history of exposure to SARS-CoV-2 infection, date of diagnosis and onset of symptoms, the first case in the family cluster were collected. In addition, pediatricians from 9 hospitals throughout Greece were invited to contribute details about children with COVID-19 that had been hospitalized. Any data queries were reviewed by at least 2 investigators and were clarified with the reporting center. Data were analyzed per child unless otherwise stated.

Virologic Investigation

Patients' respiratory samples were tested by real-time RT-PCR following commercial or in-house protocols. Children were categorized into 3 groups based on the PCR amplification cycle threshold (Ct) value, as high, moderate, or low viral load (Ct <25, 25–30 or >30, respectively). Samples with Ct >38 were considered negative.

Definitions

Asymptomatic SARS-CoV-2 cases were defined as those with positive SARS-CoV-2 PCR in the absence of symptoms. COVID-19 cases were defined as those with a positive SARS-CoV-2 PCR and compatible signs and symptoms. COVID-19 cases were classified as mild when patients were managed in the outpatient setting, moderate when patients were admitted to hospital and had a favorable outcome, while severe were classified those admitted to ICU or had a fatal outcome. Low-grade fever was defined as a temperature of ≥37.5°C and <38.0°C twice within 24 hours, respectively. Fever was defined as a temperature of ≥38.0°C twice within 24 hours, respectively. Febrile episode was defined as fever only. Acute respiratory infection was defined as the onset of at least one respiratory symptom (eg, cough, sore throat, dyspnea). Influenza-like illness (ILI) was defined as the onset of fever, weakness, headache and/or myalgias in association with cough, dyspnea and/or pharyngeal pain. Pneumonia was defined as a case of respiratory infection in a patient with radiographic or computer tomography findings compatible with pneumonia. Children were defined as persons <19 years of age. A family cluster was defined as the detection of at least 2 cases of SARS-CoV-2 infection within a family. First case was defined as the first COVID-19 case in a family. Household members were defined as persons living in the same residence. Close contact was defined as a contact of >15 minutes within a distance of <2 m with a COVID-19 case.

Statistical Analysis

All items were coded and scored and the data were analyzed using IBM-SPSS 26 (IBM Corp. Released 2016). Categorical variables were compared by using the chi-squared test while for continuous variables t-test was used. A logistic regression analysis was conducted to assess the characteristics that predict the hospitalization of children. Another logistic regression analysis was conducted to assess the characteristics that predict the viral load of children. *P* values <0.05 were considered statistically significant. The infamily attack rate of SARS-CoV-2 infection was estimated as follows: (number of household members with SARS-CoV-2 infection/number of household members) × 100. Notification rates were estimated using official data of the Hellenic Statistical Authority.[5]

Ethical Issues

The study was approved by the Board of Directors of the National Public Health Organization and the Ethics Committees of the hospitals where children with COVID-19 were hospitalized. Written consent was not required, given that the data were pseudo-anonymized and collected within the context of epidemiologic surveillance. Data were managed in accordance with the national and European Union laws.

RESULTS

Characteristics and Viral Loads of Children With SARS-CoV-2 Infection

A total of 203 children with SARS-CoV-2 infection were studied, which corresponds to a cumulative notification rate of 9.74 cases per 100,000 children 0–19 years old. Their median age was 11 years (range: 6 days to 18.4 years). Table 1 shows their characteristics. Of the 203 children, 111 (54.7%) had an asymptomatic infection and 92 (45.3%) developed COVID-19. Table 2 presents the distribution of children by age group and type of infection and Table 3 summarizes the characteristics of children by status of symptoms. Compared with other age groups, school-age children 6–12 years old were more likely to have asymptomatic infection (accounting for 34.2% of all asymptomatic infections), while infants <1 year were more likely to develop symptoms (accounting for 19.5% of all COVID-19 cases) (*P*-value = 0.001). Among 164 children for

TABLE 1. Characteristics of 203 Children With SARS-CoV-2 Infection, Greece, February 26 to June 30, 2020

Characteristic	N (%) (n = 203)
Median age* (range)	11 yr (6 d to 18.4 yr)
Male sex	106 (52.2)
Underlying condition†	13 (6.4)
Source of SARS-CoV-2 infection	
Family	132 (65)
Community	29 (14.3)
Travel	9 (4.4)
School	4 (2.0)
Other	4 (2.0)
Unknown	25 (12.3)
Type of SARS-CoV-2 infection	
Asymptomatic	111 (54.7)
COVID-19	92 (45.3)
Mild	68 (73.9)
Moderate	23 (25.0)
Severe	1 (1.1)
Viral load‡	
High	46 (28.1)
Moderate	44 (26.8)
Low	74 (45.1)

*At time of diagnosis of SARS-CoV-2 infection.

†Chronic respiratory disease (3), chronic cardiovascular disease (2), obesity (2), chronic neurologic disease (1), chronic hepatic disease (1), chronic renal disease (1), malignancy (1), pregnancy (1), prematurity (1).

‡Of 164 children for whom the cycle thresholds were available.

TABLE 2. Type of SARS-CoV-2 Infection by Age Group of 203 Children, Greece, February 26 to June 30, 2020

	Asymptomatic	Mild	Moderate	Severe	Total
Age Group (yr)	(N = 111)	(N = 68)	(N = 23)	(N=1)	(N = 203)
<1	5 (21.7)	6 (26.1)	11 (47.8)	1 (4.4)	23
≥1–6	21 (53.8)	13 (33.4)	5 (12.8)	0 (0)	39
>6–12	38 (67.8)	16 (28.6)	2 (3.6)	0 (0)	56
>12–<19	47 (55.3)	33 (38.8)	5 (5.9)	0 (0)	85

TABLE 3. Characteristics of Children With SARS-CoV-2 Infection by Presence of Symptoms, Greece, February 26 to June 30, 2020

	Asymptomatic	COVID-19	
Characteristic	N = 111	N = 92	*P*
Mean age ± SD (years)	10.78 ± 4.98	9.75 ± 6.81	0.230
Age group (years)			0.001
<1	5 (4.6)	18 (19.6)	
≥1–6	21 (18.9)	18 (19.6)	
>6–12	38 (34.2)	18 (19.6)	
>12–<19	47 (42.3)	38 (41.2)	
Male sex	62 (55.9)	44 (47.8)	0.254
Underlying condition	6 (5.5)	7 (7.6)	0.534
Viral load*			0.978
Low	39 (44.8)	35 (45.5)	
Moderate	23 (26.4)	21 (27.3)	
High	25 (28.7)	21 (27.3)	

*Of 164 children for whom the cycle thresholds were available.

whom the Ct values were available, 46 children (28.1%) had high viral load, 44 (26.8%) moderate and 74 (45.1%) low viral load.

There was no significant difference between children with asymptomatic infection and children with COVID-19 in terms of mean age, sex, underlying condition and viral load (Table 3). Furthermore, there was no significant difference between the 3 groups of viral load in terms of mean age, distribution per age groups, sex, underlying condition, occurrence of fever and hospitalization rate, even when children with moderate and high viral loads were grouped together (data not shown). A logistic regression analysis conducted to assess the association between age group, sex, having an underlying condition, the category of infection, hospitalization and viral load, found that none of these variables predicted viral load (data not shown).

Table 4 shows the signs and symptoms of the 92 children with COVID-19. Fever was the most prevalent symptom (42 children; 45.6%) followed by low-grade fever (26 children; 28.3%). Children had fever for a median duration of 2 days (range: 1–10 days). In terms of clinical syndromes, 45 children (48.9%) had an acute respiratory infection, 28 children (30.4%) had an ILI and 25 (27.2%) had a febrile episode.

Hospitalized Children With COVID-19

Twenty-four children with COVID-19 (26.1%) were hospitalized. Table 5 shows their characteristics. Median age was 12.2 months (range: 6 days to 18.4 years) and 12 hospitalized children (50%) were younger than 12 months of age. Pneumonia was diagnosed in 7 of 19 (29.2%) children who underwent a chest radiograph, while an 18-year-old adolescent had chest radiographic findings suggestive of acute respiratory distress syndrome. Five children required supplemental oxygen. An infant with chronic neurologic disease (spinal muscular atrophy type II) was admitted to a pediatric ICU, required mechanical ventilation, underwent tracheostomy, gradually improved but was still hospitalized by the end of the study period because of her underlying disease. The median length of hospitalization of the remaining 23 children was 4.5 days (range: 1–13 days). Six children were treated with hydroxychloroquine, while lopinavir/ritonavir was used in 2 adolescents. The infant in ICU was treated with hydroxychloroquine, azithromycin, oseltamivir and systemic steroids. In all other children, all symptoms resolved without apparent sequelae. No fatal outcome was reported. A logistic regression analysis found that the only variable that predicted hospitalization was being <5 years old (*P*-value = 0.006). Sex, having an underlying condition, the category of SARS-CoV-2 infection, and viral load were not associated with a significant risk for hospitalization (data not shown).

TABLE 4. Signs and Symptoms of Children With COVID-19, Greece, February 26 to June 30, 2020

	N (%)
Signs/symptoms	N = 92
Fever	42 (45.6)
Low-grade fever	26 (28.3)
Runny nose	25 (27.5)
Cough	24 (26.1)
Headache	17 (18.5)
Sore throat	11 (12)
Diarrhea	10 (10.9)
Loss of taste and/or smell	9 (9.8)
Weakness	9 (9.8)
Myalgia	8 (8.8)
Dyspnea	7 (7.6)
Nausea/vomiting	5 (5.4)
Arthralgia	4 (4.3)
Abdominal pain	2 (2.2)
Restlessness/irritation	1 (1.1)

TABLE 5. Characteristics of Children and Adolescents Hospitalized With COVID-19, Greece, February 26 to June 30, 2020

	N (%)
Characteristic	N = 24
Median age* (range)	12.2 m (6 d to 18.4 yr)
Age group* (years)	
<1	12 (50)
≥1–6	5 (20.8)
>6–12	2 (8.3)
>12–<19	5 (20.8)
Male sex	12 (50)
Underlying condition†	6 (21.7)
ICU admission	1 (0.4)
Fatal outcome	0 (0)

*At time of diagnosis of SARS-CoV-2 infection.

†Chronic respiratory disease (1), chronic cardiovascular disease (1), obesity (2), chronic neurologic disease (1), prematurity (1).

Epidemiologic Investigation

The epidemiologic investigation revealed that transmission from a household member accounted for 132 of 178 (74.2%) pediatric cases with SARS-CoV-2 infection for which the source of infection was identified (Table 1). Two 18-year-old adolescents

lived alone. The remaining 201 children corresponded to 133 families with a median of 5 household members (range: 1–16 members) per family and a median of 2 children (range: 1–6 children) per family. In total there were 979 household members in the 133 families, of whom 428 (43.7%) had a laboratory-confirmed SARS-CoV-2 infection, including 112 mothers, 97 fathers, 156 siblings, 39 grandparents, 11 uncles/aunts, 8 cousins, 3 housemaids, 1 husband and 1 partner. The median attack rate of SARS-CoV-2 infection was 40% (range: 11.1%–100%) per family. At least one more household member was tested positive for SARS-CoV-2 infection in 146 pediatric cases (71.9%), while a median of 2 additional household members (range: 0–8 members) were tested positive per family. An adult was the first case of SARS-CoV-2 infection in the families of 125 (66.8%) children with SARS-CoV-2 infection, while 62 children (33.2%) were identified as first or single cases of SARS-CoV-2 infection in their families. Of the abovementioned 62 children, 51 children had no other family member infected, 1 child had an unknown family history, and 10 children had at least 1 family member with SARS-CoV-2 infection. In particular, there were 2 siblings who developed symptoms and tested positive for SARS-CoV-2 33 days apart while both parents were negative; 2 siblings who developed symptoms and tested positive concomitantly while both parents were negative; one family of 4 (2 siblings and both parents) and one family of 3 (child and both parents) tested positive through massive screening in a highly endemic region (in both families the children were tested first while the source of SARS-CoV-2 infection remained unknown); 1 family of 4 (2 siblings and both parents) tested positive following exposure in the community (the children were tested first); and one 18-year-old adolescent boy whose mother and his 16-year-old sister were found positive for SARS-CoV-2 but it was unclear from whom he got infected. In this latter family, there was evidence of transmission of SARS-CoV-2 infection from the 16-year-old girl to her mother. There was no other evidence of transmission from a child to an adult or from a child to another child. Overall, transmission occurred from an adult to a child in 133 families. Lastly, in terms of timing of infection, 29 pediatric cases (14.3%) occurred before school closure (March 11), 19 cases (9.3%) after school closure but before the nationwide lockdown (March 23), 70 cases (34.5%) during the nationwide lockdown (March 23 to May 3) and 85 cases (41.9%) after the lifting of the lockdown (May 4 to June 30). The schools reopened gradually (depending on the grade of the students) from May 11 to June 1, and closed for summer time on June 15. Students attended physically the schools every other day.

DISCUSSION

Understanding the characteristics of SARS-CoV-2 infection of children in one country and their role in the ongoing COVID-19 pandemic is crucial to guide public health interventions including screening, school closures, use of masks, and future vaccination guidelines when COVID-19 vaccines become available. We studied 203 children and adolescents consecutively diagnosed with SARS-CoV-2 infection in Greece. To the best of our knowledge, this is one of the largest cohorts of children with SARS-CoV-2 infection and their viral loads published so far.

More than half of our children had an asymptomatic SARS-CoV-2 infection, which is in line with studies from China.[3,4,6,7] We have to keep in mind however, that the criteria for testing for SARS-CoV-2 have changed during the pandemic in Greece as elsewhere. As a result, it is difficult to draw quantitative inferences about the distribution of asymptomatic infections versus COVID-19. In our series, infected school-age children 6–12 years old were more likely to be asymptomatic compared with other pediatric age groups, accounting for one-third of all asymptomatic infections. Moreover, infants <1 year accounted for 19.5% of all COVID-19 cases and 50% of all hospitalized cases, which may be partially attributed to the increased awareness of pediatricians and parents and healthcare seeking for ill infants. Similarly, infants <1 year accounted for 16.5% of 406 children with COVID-19 in China,[4] and infants <2 years accounted for 40% of 585 pediatric cases hospitalized in 77 healthcare facilities across Europe.[8] In our series, approximately one-third of children with COVID-19 presented with an ILI, which points to the importance of influenza vaccination during the upcoming influenza season, to reduce the possibility of influenza and avoid diagnostic dilemmas and inappropriate management in terms of antiviral therapy and infection control.[9] As also reported by others,[4,10] our children had a favorable outcome and no death occurred. There was no case of Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 recorded by the participating hospitals most likely due to the rather limited SARS-CoV-2 transmission in the community and the small number of children infected. A recent study conducted in the New York State in the USA estimated its rate at about 1:161 COVID-19 cases among persons under 21 years of age in the studied population.[11]

In accordance with studies from China and Switzerland and a study of family clusters of SARS-CoV-2 infection of ours,[4,10–12] in the current study, adults were the primary source of SARS-CoV-2 infection in families, while their contribution to virus spread within families was high. In particular, an adult household member was the source of infection in two-thirds of our cases. This could be attributed to the fact that children are asymptomatic in a higher proportion than adults, and thus less often tested than the latter, unless as secondary cases. However, in our study, almost two-thirds of the pediatric cases occurred out of the lockdown period, yet children were mainly infected by an adult family member and not vice versa. Transmission of SARS-CoV-2 from children to adults has been occasionally reported.[4] In our series, there was only one case of transmission of infection from an adolescent with COVID-19 to her mother, while we found no evidence of child-to-child transmission. Similarly, the investigation of a cluster of COVID-19 that occurred in France found no case of transmission of infection from an infected symptomatic child, despite the fact that the child had many close contacts with his classmates in 3 different schools.[13] The fact that children with SARS-CoV-2 infection are often asymptomatic or have a mild illness (which translates to fewer opportunities to expel and spread the virus) compared with adults may partially explain this finding.[12] However, in a large cohort of 59,073 contacts of 5706 COVID-19 cases across all age groups in South Korea, the highest COVID-19 rate (18.6%) was found among household contacts of school-age children and the lowest among children 0–9 years old (5.3%).[14]

We found a median attack rate of SARS-CoV-2 infection of 40% in families with an infected child, which extended up to 100% in some families. Within families, attack rates as high as 75% have been reported in other studies.[6,12,15,16] In the large cohort of 59,073 contacts in South Korea, it was estimated that 11.8% of household contacts developed COVID-19 compared with 1.9% of non-household contacts, which underlines the transmission dynamics of SARS-CoV-2 within households.[14]

There are scarce data on the association between viral loads of SARS-CoV-2 and infectivity as well as clinical manifestation and course of illness. A recent study of 145 patients with mild or moderate COVID-19, found that children <5 years had significantly lower median Ct values than children 5–17 years old or adults, which indicates that young children have equivalent or higher viral loads in their upper respiratory tract compared with older children and adults.[17] Significantly lower Cts have been found in severe than in mild COVID-19 cases at the time of admission and at or beyond

day 10 of illness, suggesting that higher and more prolonged viral loads might be associated with severe clinical outcomes.[18] In our study, most children had moderate or high viral loads. However, we found no correlation between the Ct values and age or severity of SARS-CoV-2 infection. Symptomatic children had higher viral loads in nasopharyngeal swab specimens than asymptomatic children in one study,[19] yet no correlation has been found between viral loads and disease presentation by others.[20] Two recent studies found that children with SARS-CoV-2 infection have viral loads comparable with those in adults, rendering transmission plausible.[20,21] Host or other factors could explain the discrepancies between viral loads in upper respiratory tract of children and their contribution to virus transmission.

A limitation of the current study was the fact that the criteria for testing for SARS-CoV-2 infection and for hospitalization may have changed during the study period. The fact that Ct values correspond to viral nucleic acid and not necessarily to infectious virus should also be considered. Recall bias about in-family transmission events is also possible. An advantage of the current study is the large number of consecutively diagnosed children and adolescents with SARS-CoV-2 infection retrieved from the national surveillance database.

In conclusion, the large number of children with SARS-CoV-2 infection collected nationwide allowed us to study the epidemiologic and clinical profiles of SARS-CoV-2 infections during infancy, childhood and adolescence. In our setting adults appear to play a key role in introduction and spread of the virus in families, while there was only one case of transmission from an adolescent to an adult family member. This is in contrast to the fact that children manifest high and moderate viral loads regardless of age, onset of symptoms or severity of infection. Further studies are needed to elucidate the role of young patients in the ongoing pandemic and particularly in light of the reopening of schools and the need to prioritize groups for future COVID-19 vaccination.

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Greek Study Group on SARS-CoV-2 Infections in Children: Karolina Akinosoglou (Department of Internal Medicine, University of Patras Medical School, Patras); Dimitrios C. Cassimos (Department of Pediatrics, Democritus University of Thrace, Alexandroupolis); Konstantina G. Gartsonika (Microbiology Laboratory, University of Ioannina, Ioannina); Georgia Gioula and Maria Exindari (Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki); Charalambos Gogos (Department of Internal Medicine, University of Patras Medical School, Patras); Ioanna Grivea (Department of Pediatrics, University of Thessaly, Larissa); Elias Iosifidis and Parthena Savvidou (Third Department of Pediatrics, Aristotle University School of Health Sciences, Thessaloniki); Dimitrios Karapiperis (424 General Military Hospital, Thessaloniki); Athanasios Kossyvakis and Aspasia Kontou (National Reference Laboratory for Influenza and other Respiratory Viruses, Hellenic Pasteur Institute, Athens); Symeon Metallidis (First Department of Internal Medicine, Division of Infectious Diseases, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki); Athanasios Mitsianis (Mpodosakeio General Prefecture Hospital of Ptolemaida, Ptolemaida); Maria Noni ("Aghia Sophia" Children's Hospital, Athens), Kalliopi Papadima and Kassiani Gkolfinopoulou (National Public Health Organization, Athens); Nikolaos Spanakis and Elisavet Froukala (Department of Microbiology, Medical School, National and Kapodistrian University of Athens, Athens); Vasiliki Spoulou (University of Athens First Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens); Nikolaos Spyridis ("Aglaia Kyriakou" Children's Hospital, Athens); Garyfallia Syridou (Third Department of Pediatrics, National and Kapodistrian University of Athens).

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