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Stefania Bellino, PhD, Ornella Punzo, MD, PhD, Maria Cristina Rota, MD, Martina Del Manso, DStat, Alberto Mateo Urdiales, MD, Xanthi Andrianou, PhD, Massimo Fabiani, DStat, Stefano Boros, Mr, Fenicia Vescio, MD, Flavia Riccardo, MD, Antonino Bella, DStat, Antonietta Filia, MD, PhD, Giovanni Rezza, MD, Alberto Villani, MD, PhD, Patrizio Pezzotti, DStat, and the COVID-19 Working Group

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COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy

Stefania Bellino[a*], PhD, Ornella Punzo[a*], MD, PhD, Maria Cristina Rota[a], MD, Martina Del Manso[a], DStat, Alberto Mateo Urdiales[a], MD, Xanthi Andrianou[a], PhD, Massimo Fabiani[a], DStat, Stefano Boros[a], Mr, Fenicia Vescio[a], MD, Flavia Riccardo[a], MD, Antonino Bella[a], DStat, Antonietta Filia[a], MD, PhD, Giovanni Rezza[b], MD, Alberto Villani[c], MD, PhD, Patrizio Pezzotti[a], DStat, and the COVID-19 Working Group[§]

Affiliations: [a]*Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy*
[b]*General Directorate for Prevention, Ministry of Health, Rome, Italy*
[c]*General Pediatrics and Infectious Diseases Unit, Pediatric Hospital Bambino Gesù, Rome, Italy*

**Contributed equally as co-first authors*

Address correspondence to: Stefania Bellino, Department of Infectious Diseases, Istituto Superiore di Sanità, viale Regina Elena, 299, 00161, Rome, Italy [stefania.bellino@iss.it].

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Abbreviations: Coronavirus disease-2019 (COVID-19), Severe acute respiratory syndrome coronavirus (SARS-CoV).

Table of Contents Summary
The study was aimed at describing the epidemiological and clinical characteristics of COVID-19 cases in children and adolescents in Italy.

What's Known on This Subject
Although COVID-19 is less frequent and often less severe in children compared to adults, limited data exists on risk factors for disease severity and death in pediatric patients.

What This Study Adds
The present study describes pediatric cases (persons aged <18 years) of SARS-CoV-2 infection in Italy and compares them to adult and elderly patients. Underlying medical conditions and younger age represent risk factors for disease severity among children and adolescents.

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Contributors' Statement Page

Dr Bellino performed the statistical analyses and drafted the manuscript; Dr Punzo contributed to collect the clinical data and drafted the manuscript; Drs Rota, Filia, Rezza, and Prof. Villani critically reviewed the manuscript; Drs Del Manso, Mateo Urdiales, Andrianou, Fabiani, Vescio, and Mr Boros contributed to collect the data and carried out the final database; Dr Riccardo contributed to the coordination of the COVID-19 national surveillance; Dr Bella *coordinated and supervised the surveillance data collection*; Dr Pezzotti is the head of the Italian COVID-19 surveillance system and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Objective: To describe the epidemiological and clinical characteristics of Coronavirus disease-2019 (COVID-19) pediatric cases aged below 18 years in Italy.

Methods: Data from the national case-based surveillance system of confirmed COVID-19 infections until May 8, 2020, were analyzed. Demographic and clinical characteristics of subjects were summarized by age groups (0-1, 2-6, 7-12, 13-18 years), and risk factors for disease severity were evaluated using a multilevel (clustered by region) multivariable logistic regression model. Furthermore, a comparison among children, adults and elderly was performed.

Results: Pediatric cases (3,836) accounted for 1.8% of total infections (216,305), the median age was 11 years, 51.4% were males, 13.3% were hospitalized, and 5.4% presented underlying medical conditions. The disease was mild in 32.4% of cases and severe in 4.3%, particularly in children ≤6 years old (10.8%); among 511 hospitalized patients, 3.5% were admitted in Intensive Care Unit (ICU), and four deaths occurred. Lower risk of disease severity was associated with increasing age and calendar time, whereas a higher risk was associated with pre-existing underlying medical conditions (OR=2.80, 95% CI 1.74-4.48). Hospitalization rate, admission in ICU, disease severity, and days from symptoms onset to recovery significantly increased with age among children, adults and elderly.

Conclusions: Data suggest that pediatric cases of COVID-19 are less severe than adults, however, age ≤1 year and the presence of underlying conditions represent severity risk factors. A better understanding of the infection in children may give important insights into disease pathogenesis, health care practices and public health policies.

Introduction

The infection caused by the new severe acute respiratory syndrome coronavirus (SARS-CoV-2), associated to Coronavirus disease-2019 (COVID-19), characterized by severe pneumonia in a variable proportion of cases, was first reported in the city of Wuhan[1-3] China, in December 2019 and then spread across continents; first cases were initially diagnosed in Italy in late January in people coming from China.[4]

After the detection of the first locally-acquired case of SARS-CoV-2 infection in the Lombardia region (Northern Italy) on February 20,[4] the number of cases and deaths during the subsequent weeks increased rapidly.[5] Despite the high number of diagnosed subjects, children are still a small proportion of the cases in Italy[6]. This is likely due to several factors, as children are

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expected to experience a milder disease,[7] testing strategies privilege frankly symptomatic cases[8,9] and, due to high incidence, focused on severely symptomatic patients, especially in the intensely-hit northern regions in Italy.

The Chinese Center for Disease Control and Prevention reports that, of the 72,314 cases reported as of February 11, 2020, in China, only 2% were in individuals of less than 19 years of age.[7] Children appear to be less commonly affected by SARS-CoV-2 infection than adults, and to be more commonly asymptomatic,[7] however, in some cases they can develop complications, particularly infants.[10] To date, data on clinical features and risk factors for disease severity and death in infants, children, and adolescents are still limited, as well as a comparison with adults for differences in clinical characteristics, disease progression, and outcome.

The objective of the present study is to describe the epidemiological and clinical characteristics of COVID-19 in individuals less than 18 years old in Italy and compare them to adults and the elderly.

Methods

Study population

The study population included children aged <18 years with laboratory-confirmed COVID-19, reported to the Italian integrated Covid-19 surveillance system.

According to the Italian case definition[11-13], all patients presenting to the healthcare system with symptoms compatible with COVID-19 infection or with an epidemiological link (close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms, or having been a resident or a staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed), hospitalized

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patients with severe acute respiratory infections, and high-risk healthcare workers should be tested for SARS-CoV-2 virus.[11-13] The case definition considers as a confirmed case any person with laboratory confirmation of SARS-Cov-2 virus, irrespective of clinical signs and symptoms.[11-13]

Study outcomes

The primary outcomes of the study were to outline the epidemiological and clinical characteristics of COVID-19 pediatric patients in Italy, to investigate the disease severity risk factors, and compare children and adolescents to adults and the elderly.

The clinical state was defined according to the following classification: asymptomatic (no apparent signs or symptoms of disease); paucisymptomatic (dry cough, general malaise, low-grade fever, tiredness); mild (uncomplicated upper respiratory tract viral infection, (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging; severe (e.g. pneumonia, hypoxia dyspnea, tachypnea requiring hospitalization); critical (e.g. severe pneumonia, acute respiratory distress syndrome, septic shock, and/or multiple organ dysfunction requiring hospitalization in intensive care). However, in several cases the information about the severity of the disease was missing or the case was reported by the Regions as “symptomatic”. Recovery was defined as resolution of clinical symptoms with two negative RT-PCR tests from respiratory specimens at 24 hours interval.[14]

The Italian integrated COVID-19 surveillance system

With the aim to monitor the epidemic in Italy and support the planning of public health actions, a case-based surveillance system was established on February 27, 2020. The system contains case-based data on all laboratory-confirmed cases of COVID-19 as per the case definition by

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the European Centre for Disease Prevention and Control regularly updated.[11-13] From the beginning of the outbreak until March, all nasopharyngeal swabs tested positive by RT-PCR at regional level were sent for confirmation to the National Reference Laboratory at the Istituto Superiore di Sanità, and re-tested according to the World Health Organization and Centers for Disease Control and Prevention protocols.[15-16] Due to the high concordance (99%) of results with the regional laboratories, the policy was then changed allowing selected reference regional laboratories, with demonstrated capacity, to directly confirm COVID-19 suspected cases, using a selected number of RT-PCR-based commercial diagnostic tests for SARS-CoV-2.[13]

Data sources

Data from the Italian case-based surveillance system of confirmed SARS-CoV-2 infections until May 8, 2020, collected from all 21 regions and autonomous provinces, were analyzed, considering cases aged less than 18 years who tested positive for SARS-CoV-2. The national surveillance system is coordinated by the Istituto Superiore di Sanità, and data were collected using a secure online platform or received as individual datasets (from three regions) to be included in a single database. Data collected on all laboratory-confirmed cases include information on demographics, clinical severity, underlying medical conditions, date of symptoms onset, date of diagnosis, date of hospitalization, clinical outcome, region of diagnosis, and province of residence. Information on underlying conditions was collected based on anamnestic data, according to the following categories: cardiovascular, respiratory, oncologic, neurological, liver, and renal diseases, metabolic disorders, diabetes, immune deficiency, obesity. Details on the four deaths that occurred in children were retrieved from the medical records.

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The study was conducted as part of public health and surveillance activities for the COVID-19 emergency. Because of the nature of aggregated data and the ongoing public health response to control the outbreak, as well as the importance of sharing the research findings, ethical approval was waived by the institutional review board.[17]

Statistical analysis

Chi-squared test for categorical variables and Kruskal Wallis test for continuous variables were used to compare cases among age groups for demographic and clinical characteristics.
The absolute number of pediatric cases was aggregated by regions/autonomous provinces as well as the cumulative incidence (per 100,000 inhabitants), calculated using population estimates aged <18 years for 2019 available from the Italian National Institute of Statistics; four areas were detected based on the quartiles of the national distribution of the pediatric population (low, medium, high, very high). In addition, based on the severity of COVID-19 (considering the highest severity between baseline and follow-up), risk factors for mild/severe/critical outcome vs asymptomatic/paucisymptomatic clinical state were evaluated using a multilevel (clustered by region) multivariable logistic regression model, including sex, age groups (0-1, 2-6, 7-12, 13-18 years), presence of pre-existing underlying medical conditions, and calendar time: February 20-March 23 (the first month of the epidemic), March 24-April 15 (three weeks after the peak of the epidemic), and April 16-May 8 (the last three weeks of observation during the declining phase). Finally, a comparison for demographic and clinical characteristics was performed among children (<18 years), adults (18-64 years), and elderly (≥65 years), using the Chi-squared test for categorical variables and Kruskal Wallis test for continuous variables.

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Statistical analysis was carried out using the Stata software, version 16 (Stata Corporation, College Station, Texas, USA).

Results

COVID-19 epidemiology in children and adolescents

In Italy, 16% of the residents are made up of infants, children, and adolescents aged <18 years. As of May 8, 2020, this pediatric population accounted for 1.8% (3,836/216,305) of all COVID-19 reported cases at the national level, with a variable percentage across the Italian regions. Considering all cases aged <18 years with an available date of diagnosis (3,720, 97%), a continuous daily increase of the diagnosed cases from February 23 (the first reported pediatric case) until the peak of the outbreak (March 24-26) was found (two weeks after the national lockdown), whereas since then a gradual and steady decrease was observed until the first week of May (Figure 1A). An interregional variation for pediatric COVID-19 cases was observed in Italy, the highest absolute number of cases was reported in the Northern regions (Lombardia, Emilia-Romagna, Veneto, and Piemonte), the most hit by the epidemic (Figure 2A), whereas major incidence rates were detected in Autonomous Province of Trento (180.6/100,000), Valle d'Aosta (115.1 per 100,000 population), Emilia-Romagna (75.5/100,000), Abruzzo (73.8/100,000), and Autonomous Province of Bolzano (62.5/100,000) (Figure 2B).

Demographic and clinical characteristics of pediatric patients

The epidemiological history most frequently reported was a relationship with a familial cluster, followed by a contact with a confirmed case. Most cases of COVID-19 occurred in adolescents aged 13-17 years (40.1%), followed by those in children 7-12 (28.9%), 2-6 (17.2%) and 0-1

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(13.8%) years old; the median age was 11 years, and 51.4% of them were males (Table 1). The median time from symptoms onset to diagnosis increased with age, from 3 days among infants to 6 days among adolescents ($p<0.001$) as well as the median time from symptoms onset to hospitalization, from 1 day among infants to 4 days among adolescents ($p=0.001$). Overall, the hospitalization rate was 13.3%, the highest percentage of hospital admission occurred in infants aged ≤1 year (36.6%), followed by children aged 2-6 years (12.8%), 13-17 years (8.9%) and 7-12 years (8.8%) ($p<0.001$); the admission rate in Intensive Care Unit was 3.5%, with the highest value among children aged 2-6 years (9.5%) ($p=0.010$). Pre-existing underlying medical conditions increased with age from 3.6% in infants ≤1-year-old to 6.0% in adolescents 13-17 years old ($p<0.001$), and were particularly high (9.8%) among hospitalized patients; the most common were respiratory, cardiovascular and oncologic diseases. Among patients with available clinical state classification (2,015, 52% of the total), younger children, particularly infants, showed the highest proportion of severe infections ($p<0.001$); specifically, the proportions of severe/critical state were 10.8%, 6.5%, 2.4%, and 3.0% for age groups 0-1, 2-6, 7-12, 13-17 years old, respectively (Table 1).

After adjusting for sex, age groups, underlying medical conditions, and calendar time of diagnosis, a lower risk of disease severity (mild/severe/critical as compared to asymptomatic/paucisymptomatic) was detected with increasing age compared to infants ≤1-year-old [2-6 years Odds Ratio (OR)=0.30, 95% Confidence Interval (CI) 0.20-0.46; 7-12 years OR=0.22, 95% CI 0.15-0.33; 13-17 years OR=0.26, 95% CI 0.18-0.37]; whereas a higher risk was associated with the presence of at least one pre-existing underlying medical condition (OR=2.80, 95% CI 1.74-4.48). The second period after the peak of the outbreak was associated with a lower risk of disease severity as compared to the first month (February 23-March 23) of

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the epidemic (OR=0.61, 95% CI 0.47-0.80 March 24-April 15; OR=0.33, 95% CI 0.23-0.46 April 16-May 8); moreover, high interregional variation was observed, and approximately half of the disease severity variability was attributable to the region effect (Table 2).

COVID-19 related deaths in children

Four deaths were reported in children, and clinical details are described below.

The first case was a 5-year-old girl who died in hospital with SARS-CoV-2 pneumonia. The patient had a type-2 mucolipidosis (an inherited metabolic disease) associated with hypertrophic cardiomyopathy with thickening of the mitral and aortic valves and sleep apnea syndrome. The patient was treated with antibiotics and corticosteroids, then oxygen was added, but when the general conditions deteriorated a palliative care protocol was started. The second case was an infant aged 2 months with Williams syndrome, a rare multisystemic genetic disease of neurological development, characterized by typical facial features, heart disease (especially supra-valvular aortic stenosis), cognitive, developmental and connective tissue abnormalities (joint laxity). The infant presented stenosis and hypoplasia of the pulmonary arteries and supravalvular aortic stenosis. He was admitted for cardiac surgery, and underwent a complex surgical procedure. Even though he survived the procedure, he remained on extracorporeal membrane oxygenation and could never be weaned from that in the following days, and finally died after 10 days since the surgery. The third case was an infant aged 6 months with a rare and aggressive form of cancer, i.e. an extrarenal malignant rhabdoid tumor, who underwent ten cycles of chemotherapy, developed fever associated to neutropenia and pneumonia. The last case was a 6-year-old girl who suffered from heart failure and underwent a mitral annuloplasty due to severe mitral insufficiency and left ventricular dysfunction. This hospitalization was associated with a series of complications, consisting of superinfection and deterioration of cardiac failure.

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Based on medical records and from the treating physicians' notes, all 4 children died of a deterioration of very compromised conditions, and to a certain extent the impact of SARS-CoV-2 infection may have aggravated the situation, but does not seem to be the underlying cause of death.

Comparison among pediatric, adult, and elderly populations

Evolution of the reported COVID-19 cases in Italy followed a similar trend among children (<18 years), adults (18-64 years) and elderly (≥65 years) from February to May (Figures 1A-B). More females were affected by COVID-19, except for those aged <18 years ($p<0.001$) (Table 3); males showed more severe symptoms compared to females ($p<0.001$) among adults and elderly, whereas no sex difference was found among children. Hospitalization rate significantly increased with age ($p<0.001$), indeed 13.3% of children were hospitalized compared to adults (28.3%) and elderly (49.9%), and among hospitalized patients, adults (13.0%) were the most admitted in Intensive Care Unit ($p<0.001$) as compared to children (3.5%) and elderly (10.2%) (Table 3). Disease severity also significantly increased with age ($p<0.001$), 4.2% of children had severe or critical symptoms, compared to adults (17.2%) and elderly (41.1%), whereas 63.4% of children were asymptomatic or paucisymptomatic, compared to adults (44.0%) and elderly (27.3%). About half of patients recovered within one month from the onset of the disease; the recovery rate was higher in children (38.6%) and adults (41.9%) compared to the elderly (20.2%) ($p<0.001$). Moreover, a shorter period from symptoms onset to hospitalization and recovery was found among children compared to older ages ($p<0.001$). In general, pediatric patients with COVID-19 had a good prognosis although four deaths occurred, whereas the mortality rate was 5.8% among adults with underlying medical conditions and 25.8% among the elderly.

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Discussion

This is the first large study offering a comprehensive picture of the pediatric population diagnosed with SARS-CoV-2 infection in Italy. After the first indigenous case of COVID-19 diagnosed on February 20, the number of cases rapidly increased nationwide until the peak of the epidemic, which occurred about two weeks after the national lockdown declared on March 11. A steady and gradual decrease has been observed since March 26, however, data referred to the last week of observation (May 2-8) might be influenced by reporting delay of the more recently diagnosed cases. Of note, the median delay between the date of symptoms onset and the date of the positive test result in the three study periods was 3, 5, and 9 days respectively.

As of May 8, 2020, just after the start of the lockdown easing in Italy, patients <18 years old accounted for 1.8% of all COVID-19 reported cases. This relatively low burden among children has been observed also in other countries,[18,19] however, the age distribution might reflect testing policies and case definitions, which usually include the presence of symptoms; moreover, it may be possible that the small proportion of infected children reflects a lower risk of younger subjects developing disease symptoms. Of note, a survey conducted in the municipality of Vo' in Italy, revealed a prevalence of SARS-CoV-2 infection of 2.6% in the population, and 43.2% of the confirmed cases were asymptomatic.[20] At the national level, the disease cumulative incidence rate was 40/100,000 and 419/100,000 in subjects aged <18 and ≥18 years, respectively. The distribution of pediatric cases varied throughout the country, with most of them concentrated in northern Italy, however, differences in incidence rates may be due to different testing strategies implemented at the local level (i.e. children with a more serious infection are more likely to be tested), or to existing specific clusters. Furthermore, children were usually diagnosed with COVID-19 after exposure to an infected adult within the family circle. Children of all ages were

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found positive to COVID-19 suggesting that susceptibility is always present. Clinical manifestations were less severe than in adults, however, among pediatric patients, younger children were more vulnerable, particularly infants aged ≤1 year who were hospitalized in about a third of cases; instead, children aged 2-6 years were the most frequently admitted in Intensive Care Unit.

Lower risk of disease severity was detected with increasing age, whereas a higher risk was associated with the presence of pre-existing underlying medical conditions. Moreover, our study highlighted that the second period of the outbreak was associated with a lower risk of severe disease. Indeed, the percentage of pediatric patients with severe/critical symptoms slightly decreased over time from 5.4% in the first month of the outbreak to 3.5% during the last three weeks of the observation period, as well as patients with mild symptoms, from 43.4% to 28.9%. Nevertheless, this seems more due to the effect of the phase of the epidemic (during the peak of the outbreak only subjects with clear signs and symptoms of the disease were tested) and probably to a more efficient health care provision due to a decreasing number of cases in the second phase rather than to a change in the pathogenicity of the SARS-CoV-2. The shifts of COVID-19 in terms of clinical presentation and outcome as the disease moved out from China into Europe and the rest of the world is still under debate, however, our data support the hypothesis that the disease course and severity have not undergone major changes. The evolution of the virus throughout the pandemic is not occurring faster than expected compared to other viruses during an outbreak.[21] Different clades are emerging as COVID-19 spread worldwide, and a study that performed genetic analyses of eighty-six complete or near-complete genomes of SARS-CoV-2 from twelve countries revealed many mutations and deletions on coding and non-coding regions.[22] This provided evidence of the genetic diversity and evolution of this novel

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coronavirus, although it does not mean that the emerged new strains are more pathogenic than others circulating right now.[21]

Our findings are in line with published studies describing the epidemiology of COVID-19 among pediatric patients in China[19,23] and the United States,[24] in terms of percentage of children on the overall population, clinical severity, hospitalization, and outcome.

As reflected in our analysis, previous studies also showed that children of all ages are susceptible to SARS-CoV-2 infection, but they seem to be less affected than the adult population, besides presenting with milder symptoms.[23,25,26] Although a minority of children with COVID-19 require hospitalization, severe cases have been reported.[10,27] Moreover, although children are most commonly infected through familial clusters, they were less likely to become positive, when exposed, than adults.[28] Concerning the disease severity, especially for the more severe cases, our data were comparable with a study on 2,135 children from China including 728 laboratory-confirmed cases, which found that 5% were severe (presenting hypoxemia, dyspnea, central cyanosis), and less than 1% were critical (with respiratory failure, acute respiratory distress syndrome, shock).[23]

It is unclear why children showed milder symptoms of COVID-19. A cytokine storm has been involved in the pathogenesis of severe forms of the disease in adults,[29] therefore, *one possible* explanation could be a weaker immune response to SARS-CoV-2 in children compared to adults. Other hypotheses take into account a possible viral "competition" in the respiratory tract of young children and the expression of the angiotensin-converting enzyme (ACE) 2 receptor. In the first scenario, viral interference may lead to a lower viral load in children. As for the ACE 2 receptor, it acts as the receptor for SARS-CoV-2 and it may be expressed differently in the respiratory tract of children compared to adults.[30,31]

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A recent study showed that the viral load of symptomatic and asymptomatic patients were similar, and asymptomatic patients can still infect others.[32] These "silent patients" may remain undiagnosed and be able to spread the disease to large numbers of people.[33] However, the extent to which children can act as sources of infection is still under debate, also due to the physical distancing and the schools' closure.

Of note, the European Centre for Disease Prevention and Control is closely following the information about the emergence of a post-inflammatory syndrome in children in Europe, with a possible connection to COVID-19,[34] and on May 15, 2020, the World Health Organization gave a preliminary case definition due to the urgent need for the collection of standardized data describing clinical presentations, severity, outcomes, and epidemiology.[35]

Unfortunately, the data reported in our database does not allow the identification of children with a multisystem inflammatory disorder.

Before drawing any conclusion, some limits of the study should be mentioned. In particular, the data were collected in a continuous consolidation phase and, as foreseeable in an emergency situation, some information was incomplete. Moreover, different testing strategies may have been applied regionally, since each region is responsible for planning and organizing its health services; therefore, the number of swabs per residents, as well as the ability to detect less serious cases in the period following the epidemic peak, varied in the Italian regions. Finally, we were unable to assess clinical data, such as chest radiography, pulmonary lesions, hematological and biochemical parameters, therefore, additional studies are required to understand clinical and laboratory findings associated with pediatric cases of COVID-19.

Conclusions

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Pediatric cases account for a small percentage of COVID-19 patients in Italy and disease in children was often milder than in adults. Severe disease cases in children were associated with younger age and underlying conditions. Infection control measures should be implemented to prevent COVID-19 nosocomial spread, with the need to protect vulnerable individuals and children with serious underlying conditions.

A widespread availability of testing may allow to better understand the infection in children, giving important insights into disease pathogenesis, health care practices, and public health policies.

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[§]COVID-19 Working Group: Paolo D'Ancona, Andrea Siddu, Roberta Urciuoli, Stefania Giannitelli, Paola Stefanelli, Alessandra Ciervo, Corrado Di Benedetto, Marco Tallon, (Istituto Superiore di Sanità); Regional representatives - Manuela Di Giacomo (Abruzzo), Michele La Bianca (Basilicata), Anna Domenica Mignuoli (Calabria), Angelo D'Argenzio (Campania), Erika Massimiliani (Emilia-Romagna), Tolinda Gallo (Friuli Venezia Giulia), Paola Scognamiglio (Lazio), Camilla Sticchi (Liguria), Danilo Cereda (Lombardia), Daniel Fiacchini (Marche), Francesco Sforza (Molise), Maria Grazia Zuccaro (P.A. Bolzano), Pier Paolo Benetollo (P.A. Trento), Daniela Tiberti (Piemonte), Cinzia Germinario (Puglia), Maria Antonietta Palmas (Sardegna), Salvatore Scondotto (Sicilia), Lucia Pecori (Toscana), Anna Tosti (Umbria), Mauro Ruffier (Valle D'Aosta); Filippo Da Re (Veneto).

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Table 1. Demographic and epidemiologic characteristics of individuals <18 years of age with COVID-19 in Italy, February 23-May 8, 2020.

	Class of age (years)								
	0-1		**2-6**		**7-12**		**13-17**		
	n	%	n	%	n	%	n	%	*p-value*
Total cases	528	13.8	659	17.2	1,109	28.9	1,540	40.1	
Females	245	46.4	300	45.5	542	48.9	779	50.6	*0.11*
Males	283	53.6	359	54.5	567	51.1	761	49.4	
Hospitalization	193	36.6	84	12.8	97	8.8	137	8.9	*<0.001*
Intensive care unit	5	2.6	8	9.5	1	1.0	4	2.9	*0.010*
Underling conditions	19	3.6	31	4.7	64	5.8	92	6.0	*<0.001*
Respiratory disease	0	0.0	4	12.9	9	14.1	15	16.3	*0.31*
Cardiovascular	2	10.5	3	9.7	5	7.8	7	7.6	*0.96*
Oncologic	2	10.5	3	9.7	2	3.1	4	4.4	*0.40*
Metabolic/Diabetes	1	5.3	1	3.2	3	4.7	6	6.5	*0.90*
Neurological	1	5.3	0	0.0	3	4.7	2	2.2	*0.53*
Immune deficiency	1	5.3	3	9.7	2	3.1	0	0.0	*0.04*
Disease severity									
Asymptomatic	43	20.2	141	40.1	267	44.5	334	39.3	*<0.001*
Paucisymptomatic	43	20.2	84	23.9	149	24.8	216	25.4	
Mild	104	48.8	104	29.5	170	28.3	274	32.2	
Severe	21	9.9	20	5.7	13	2.2	25	2.9	
Critical	2	0.9	3	0.9	1	0.2	1	0.1	
Recovery	322	61.0	412	62.5	654	59.0	968	62.9	*0.21*
Deaths	2	0.4	2	0.3	0	0.0	0	0.0	*0.03*
Days from symptoms to diagnosis (median, IQR)	3	(1-7)	4	(2-10)	5	(2-11)	6	(2-12)	*<0.001*
Days from symptoms to hospitalization (median, IQR)	1	(0-4)	2	(1-5)	2	(1-5)	4	(1-8)	*0.001*

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Days from symptoms to recovery (median, IQR)	28	(23-37)	27	(22-35)	29	(23-36)	32	(22-39)	*0.06*

IQR, Interquartile range. Chi-squared test for categorical variables and Kruskal Wallis test for continuous variables were used to compare the four age groups.

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Table 2. Risk factors for disease severity (mild/severe/critical vs asymptomatic paucisymptomatic) in individuals <18 years of age; multilevel multivariable logistic regression model, Italy, February 23-May 8, 2020.

	Disease severity			
Risk factors	**OR**	**95% CI**		***p-value***
Sex				
Males	*Ref.*			
Females	0.96	0.77	1.20	*0.73*
Class of age (years)				
0-1	*Ref.*			
2-6	0.30	0.20	0.46	*<0.001*
7-12	0.22	0.15	0.33	*<0.001*
13-17	0.26	0.18	0.37	*<0.001*
Underling conditions				
No	*Ref.*			
Yes	2.80	1.74	4.48	*<0.001*
Calendar time				
February 23-March 23	*Ref.*			
March 24-April 15	0.61	0.47	0.80	*<0.001*
April 16-May 8	0.33	0.23	0.46	*<0.001*
Regions (random effect)				
Variance among regions	4.18	2.04	8.59	*<0.001*
ICC (%)	56.0	38.2	72.3	

OR, Odds Ratio; CI, Confidence Interval.

ICC, intra-class correlation (proportion of variation that is attributable to the effect of clustering (Italian regions))

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Table 3. Demographic and clinical characteristics of children, adults and elderly with COVID-19 in Italy, February 20-May 8, 2020.

	Children <18 years		Adults 18-64 years		Elderly ≥65 years		
	n	%	n	%	n	%	*p-value*
Median age (IQR)	11	(5-15)	49	(39-56)	81	(73-87)	
Total cases	3,836	1.8	111,431	51.5	100,977	46.7	
Females	1,866	48.6	59,245	53.3	54,432	54.0	
Males	1,970	51.4	51,957	46.7	46,438	46.0	*<0.001*
Hospitalization	511	13.3	31,547	28.3	50,347	49.9	*<0.001*
Intensive Care Unit	18	3.5	4,115	13.0	5,127	10.2	*<0.001*
Underling conditions	206	5.4	22,570	20.2	54,412	53.9	*<0.001*
Disease severity							
Asymptomatic	785	39.0	7,959	20.0	3,539	13.0	*<0.001*
Paucisymptomatic	492	24.4	9,523	24.0	3,885	14.3	
Mild	652	32.4	15,422	38.9	8,627	31.7	
Severe	79	3.9	5,854	14.8	9,519	35.0	
Critical	7	0.3	940	2.4	1,661	6.1	
Recovery	1,480	38.6	46,665	41.9	20,346	20.2	*<0.001*
Deaths	4	0.1	2,428	2.2	26,011	25.8	*<0.001*
Days from symptoms to diagnosis (median, IQR)	5	(2-11)	6	(3-11)	6	(2-10)	*<0.001*
Days from symptoms to hospitalization (median, IQR)	2	(1-5)	7	(3-10)	5	(2-9)	*<0.001*
Days from symptoms to recovery (median, IQR)	29	(23-37)	32	(24-40)	35	(27-43)	*<0.001*

IQR, Interquartile range. Chi-squared test for categorical variables and Kruskal Wallis test for continuous variables were used to compare the three age groups.

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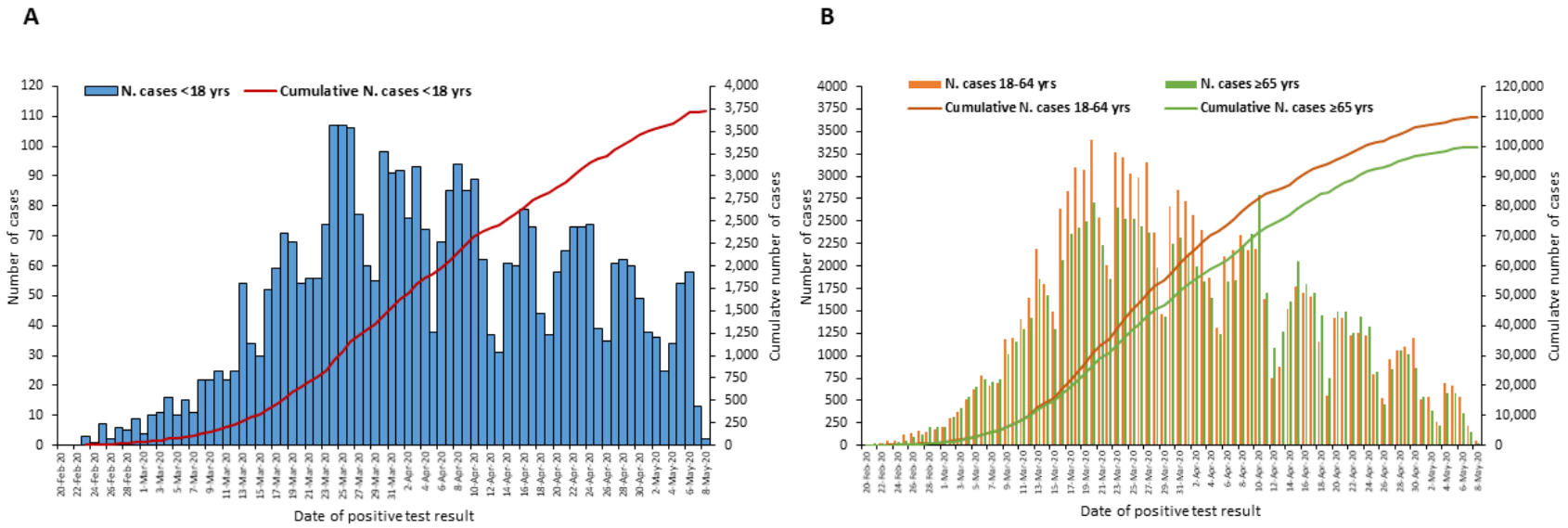

Figure 1. Epidemic curve by date of positive test result of COVID-19 cases aged <18 years (A), and aged 18-64 or ≥65 years (B), Italy, February 20-May 8, 2020.

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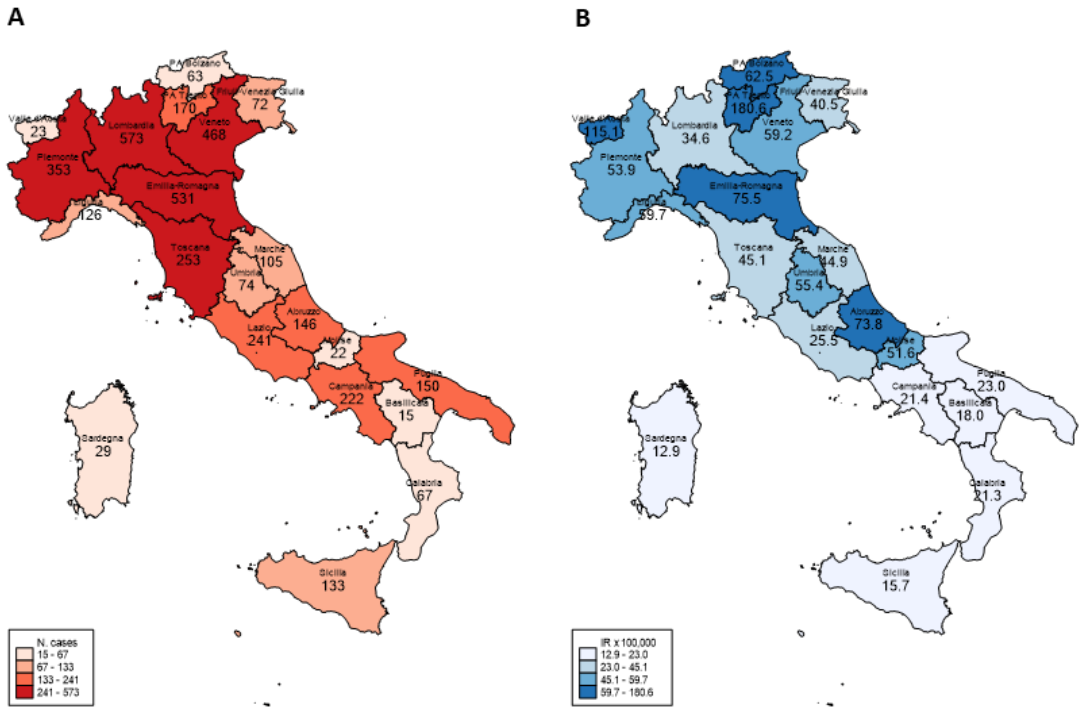

Figure 2. Absolute number (A) and incidence rates per 100,000 population (B) of COVID-19 cases aged <18 years by Italian regions/autonomous provinces of diagnosis.

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