O R I G I N A L   I N V E S T I G A T I O N S / C O M M E N T A R I E S

Characteristics and risk factors of isolated and quarantined children and adolescents during the first wave of SARS-CoV-2 pandemic: A cross-sectional study in Modena, Northern Italy

Stefania Paduano[1], Maria Chiara Facchini[1], Antonella Greco[2], Lucia Borsari[2], Valentina M. Mingrone[1], Stefano Tancredi[1,2], Elisabetta Fioretti[1,2], Giacomo Creola[1,2], Laura Iacuzio[2], Giovanni Casaletti[2], Marco Vinceti[1,3,4], Annalisa Bargellini[1], Tommaso Filippini[1,3]

[1]Department of Biomedical, Metabolic and Neural Sciences, Section of Public Health, University of Modena and Reggio Emilia, Modena, Italy; [2]Department of Public Health, AUSL Modena, Modena, Italy; [3]CREAGEN-Environmental, Genetic and Nutritional Epidemiology Research Center, Department of Biomedical, Metabolic and Neural Sciences, Section of Public Health, University of Modena and Reggio Emilia, Modena, Italy; [4]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.

Abstract. *Background and aim*: In early 2020, SARS-CoV-2 was declared a pandemic by the WHO and Italy was one of the first and most severely affected country in Europe. Despite the global interest about COVID-19 pandemic, several aspects of this infection are still unclear, especially in pediatric population. This study aims to investigate the characteristics of the isolated or quarantined children and adolescents followed by the Public Health Department of the Italian province of Modena during the first wave of COVID-19. *Methods*: The study population included all non-adult subjects aged 0-18 years who underwent isolation or quarantine during the first wave of SARS-CoV-2 pandemic from February 24 to June 18, 2020 in Modena province, Northern Italy. *Results*: In Modena province, 1230 children and adolescents were isolated in case of SARS-CoV-2 infection (6.3%), or quarantined due to close contact with confirmed cases (88.7%) or travelling from a high-risk area (5.0%). Among 349 individuals who underwent swab testing, 294 (84.2%) reported close contact with an infected cohabiting relative and 158 (45.3%) were symptomatic. Among all tested subjects, 78 (22.4%) resulted positive, with a higher proportion of symptomatic subjects compared with the SARS-CoV-2-negative (78.2% vs. 35.8%). Fever was mostly present in SARS-CoV-2-positive children (48.7% vs. 12.6%). Both anosmia (58.3% vs. 41.7%) and dysgeusia (54.5% vs. 45.5%) had only slightly higher frequency in SARS-CoV-2-positive. *Conclusions*: These findings allow to expand the knowledge regarding characteristics of non-adult subjects isolated or quarantined during the first wave of SARS-CoV-2 pandemic. (www.actabiomedica.it)

Key words: adolescent, children, contact tracing, pandemic, public health, SARS-CoV-2.

Introduction

A novel type of highly transmissible and pathogenic coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in late 2019 in China causing an acute respiratory disease, named 'coronavirus disease 2019' (COVID-19) (1,2). In early 2020, the virus spread up to be declared a pandemic by the WHO (3). Italy is one of the first and most severely affected country in Europe, with

its first indigenous case identified on February 21, 2020 (4). As a consequence, in the period February-June 2020 Italy experienced a first wave that severely affected mainly the North of the country (5,6), led to a tight lockdown (7), with regional differences possibly related to genetic, clinical, lifestyle, and environmental factors (8-15), followed by a decline in the summer period (4,5).

Soon after the beginning of the pandemic, diagnostic molecular reverse transcriptase-polymerase chain reaction (RT-PCR) tests based on swabs have been developed in order to recognize the infection status through viral RNA detection in both symptomatic and asymptomatic individuals (16). Timely diagnosis is in fact crucial to curb virus spread (17) and control its impact on the population.

COVID-19 is a potentially severe and life-threatening disease with still limited therapeutic options (18-21), and possible long-term sequalae (22,23). Still in recent months that several vaccines are available (24), the possibility of reinfection is of concern, also due to the occurrence of virus variants (25,26).

Despite the tremendous impact of the disease on the population, especially in the elderly and vulnerable subjects (27), it should be noted that COVID-19 in children is mostly a mild disease (28-31), with a very low mortality rate (32-34), although growing evidence shows that they are as susceptible to become infected as adults (35). In addition, few studies were initially carried out in children compared with the adult population and the elderly. Infected children usually show typical symptoms of acute respiratory infections, including fever and cough (29). However, differently from adults, they more likely experience extra-respiratory symptoms, diarrhea and vomiting being the most frequently reported ones (35). As a consequence, the incidence of COVID-19 may have been underestimated in children because of an initial lack of widespread testing (36).

Since the early phases of the pandemic, public health interventions have been established aiming at reducing virus spread in the population, including infection containment measures such as use of face masks and personal hygiene measures (37), closure of all non-essential activities (38) along with mobility restriction and social distancing (7). At the beginning,

also educational settings were considered at high risk of infection. For this reason, lessons in presence were suspended in schools and universities: remote learning have been activated (38) along with educational interventions for the promotion of preventive measures among teachers and students (39). As a consequence, throughout the lockdown period, children and adolescents remained at home with parents or relatives, and the transmission of SARS-CoV-2 in pediatric population primarily occurred through infected adults mainly due to household contact (28,40).

Despite the global interest and concern about COVID-19 pandemic, several aspects of this infection are still puzzling (41), especially in pediatric population characterized by much lower investigations compared to adults. In this study, we aim at investigating the characteristics of the isolated and quarantined children and adolescents followed by the Public Health Department of the Italian province of Modena during the first wave of COVID-19.

Methods

This study was approved by the 'Area Vasta Emilia Nord' Ethics Committee (approval no. AUO/0017667/20 of June 25, 2020).

Study population

Using a cross-sectional study design, we included all non-adult subjects aged 0-18 years who underwent isolation or quarantine during the first wave of SARS-CoV-2 pandemic in Modena province, Northern Italy. In particular, the study population was identified through access to the database of Public Health Department of Modena Local Health Authority. This database collects information about all children and adolescents who underwent epidemiological investigation in the period from February 24 to June 18, 2020. Children and adolescents were 'isolated' if they were confirmed as positive cases with reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection (42). Conversely, they were 'quarantined' if they were contact of infected individuals or travelling from high risk areas as assessed during

the epidemiological investigation (42). During both isolation and quarantine, children and adolescents were confined at their home in order to avoid virus transmission (43). As regards SARS-CoV-2 RT-PCR investigation, children and adolescents underwent testing when: (i) had symptoms possibly indicating COVID-19 (e.g., fever, cough, or other respiratory symptoms) and had contacts with confirmed or highly suspicious cases, mainly if they were the first suspicious cases within their family; (ii) had contact with confirmed or highly suspicious cases and attended communities or cohabited with frail people; (iii) were frail subjects in contact with confirmed or highly suspicious cases (16,44).

Data analysis

We calculated mean, standard deviation (SD), and range for continuous variables, while used absolute and relative (%) frequencies for categorical data.

All analyses have been performed in the whole study population and in selected subgroups, in particular we divided the entire sample of isolated/quarantined children into not-tested and tested for SARS-CoV-2 infection. Among this latter, we further divided according to SARS-CoV-2 positive or negative swab result. We also compared the study sample size with the overall population of Modena province (45). We used statistical software Stata v17.0 (StataCorp, College Station, TX, USA, 2021) for all data analyses.

Results

Overall in the study period from February 24 to June 18, 2020, 1230 children and adolescents were isolated or quarantined in Modena province, with a mean age of 9.6 years (SD 4.9), ranging from 0 to 17 years (Table 1). In particular, we included 599 females (48.7%) and 631 males (51.3%). Altogether, the study

Table 1. Socio-demographic characteristics of isolated/quarantined children and adolescents from Modena province during the first wave from February 24 to June 18, 2020 (n=1230). Data are number (n) and percentage (%) if not differently reported.

Characteristics	All subjects n (%)	Tested n (%)	Not tested n (%)
Overall	1230 (100)	349 (28.4)	881 (71.6)
Age†	9.6 ± 5.0	9.5 ± 5.2	9.6 ± 4.9
< 6years	311 (25.3)	99 (28.4)	212 (24.1)
6-13 years	571 (46.4)	147 (42.1)	424 (48.1)
≥14 years	348 (28.3)	103 (29.5)	245 (27.8)
Sex			
Male	631 (51.3)	174 (49.9)	457 (51.9)
Female	599 (48.7)	175 (50.1)	424 (48.1)
Isolation/quarantine reason			
Confirmed infection	78 (6.3)	78 (22.4)	0 (0.0)
Close contact	1091 (88.7)	268 (76.8)	823 (93.4)
Travelling from high-risk areas	61 (5.0)	3 (0.9)	58 (6.6)
Isolation/quarantine place			
Home	1219 (99.1)	341 (97.7)	878 (99.7)
Hospital	5 (0.4)	5 (1.4)	0 (0.0)
Hotel	2 (0.2)	2 (0.6)	0 (0.0)
Residential community	4 (0.3)	1 (0.3)	3 (0.3)
Contagion source			
Cohabiting	870 (70.7)	296 (84.8)	574 (65.2)
Non-cohabiting	360 (29.3)	53 (15.2)	307 (34.8)

Characteristics	All subjects n (%)	Tested n (%)	Not tested n (%)
Contagion context			
Cohabiting relative	865 (70.3)	294 (84.2)	571 (64.8)
Non-cohabiting relative	170 (13.8)	28 (8.0)	142 (16.1)
Recreational context	49 (4.0)	5 (1.4)	44 (5.0)
Health facility visits	24 (2.0)	1 (0.3)	23 (2.6)
School attendance	17 (1.4)	0 (0.0)	17 (1.9)
Flight	5 (0.4)	4 (1.2)	1 (0.1)
Other cohabiting subjects	3 (0.2)	2 (0.6)	1 (0.1)
Travelling from high-risk areas	2 (0.2)	0 (0.0)	2 (0.2)
Not reported	95 (7.7)	15 (4.3)	80 (9.1)
Symptoms			
Yes	239 (19.4)	158 (45.3)	81 (9.2)
No	991 (80.6)	191 (54.7)	800 (90.8)
Admitted to hospital			
Yes	9 (0.7)	9 (2.6)	0 (0.0)
No	1221 (99.3)	340 (97.4)	881 (100)
Number of siblings			
0	253 (20.5)	80 (22.9)	173 (19.6)
1	533 (43.3)	155 (44.4)	378 (42.9)
2	183 (14.9)	59 (16.9)	124 (14.1)
3	44 (3.6)	18 (5.2)	26 (3.0)
≥4	28 (2.3)	20 (5.7)	8 (0.9)
Not reported	189 (15.4)	17 (4.9)	172 (19.5)
Positive cohabitants			
0	162 (13.2)	25 (7.2)	137 (15.6)
1	651 (52.9)	176 (50.4)	475 (53.9)
2	143 (11.6)	54 (15.5)	89 (10.1)
3	45 (3.7)	34 (9.7)	11 (1.2)
4	23 (1.9)	21 (6.0)	2 (0.2)
≥5	15 (1.2)	15 (4.3)	0 (0.0)
Not reported	191 (15.5)	24 (6.9)	167 (19.0)
Index case removal			
Yes	133 (10.8)	39 (11.2)	94 (10.7)
No	1097 (89.2)	310 (88.8)	787 (89.3)

†*Mean ± standard deviation*

population corresponds to 1.06% of total non-adult individuals of Modena province (1230/116,225), with similar values in males (1.05%, 631/59,908) and females (1.06%, 599/56317). Subjects have been isolated in case of SARS-CoV-2 infection (6.3%), or quarantined due to close contact with confirmed cases (88.7%), or travelling from a high-risk area (5.0%). In the overall population, 1219 (99.1%) children have been isolated or quarantined at home. Nine patients were admitted to the hospital, nobody for COVID-19.

Exposure to SARS-CoV-2 for non-adult subjects was primarily due to contact with their relatives, mainly cohabiting (70.7%), followed by a non-cohabiting relatives (13.8%). Another relevant source of contagion was the recreational context in 4.0% of subjects (e.g., contact with a friend confirmed to be positive for SARS-CoV-2 infection), while health facility visits and school attendance were reported in 2.0% and 1.4% of subjects, respectively. Among 24 subjects related to health facility visits, 23 had the same pediatrician as index case. Most children were asymptomatic (80.6%), while 239 (19.4%) had at least one symptom.

Out of 1230 children and adolescents, 349 underwent swab testing (Table 1). Among tested participants, 294 (84.2%) reported close contact with an infected cohabiting relative, and subjects with more than one brother or sister were tested more often. All the children admitted to the hospital were tested within hospital screening schedules. Out of the 349 children and adolescents that underwent swab testing, 158 subjects (45.3%) were symptomatic (Table 2). Fever was recorded in 72 individuals (20.6%), followed by cough (17.5%). Headache, rhinorrhea and sore throat were reported in 34 (9.7%), 33 (9.5%), and 25 (7.2%) subjects, respectively. Other less frequent signs or symptoms included anosmia (3.4%),

dysgeusia (3.2%), diarrhea (3.2%), vomiting (1.7%), conjunctivitis (2.0%), asthenia (2.0%), and respiratory distress (1.7%).

Among all tested subjects, 78 (22.4%) resulted to be positive (Table 3). A higher percentage of subjects with SARS-CoV-2-positive test had three or more infected cohabitants compared to those with negative swab (61.8% vs. 10.9%). A higher proportion of symptomatic subjects were found in SARS-CoV-2-positive children and adolescents compared with the SARS-CoV-2-negative ones (78.2% vs. 35.8%).

Table 4 shows the clinical signs or symptoms of children and adolescents tested for SARS-CoV-2. Fever was the symptom mostly present in SARS-CoV-2-positive children (48.7% vs. 12.6%). Other symptoms reported by positive patients were cough (29.5%), headache (19.2%), sore throat (15.4%), and rhinorrhea (10.3%). Focusing on the 13 and 15 children with anosmia and dysgeusia, 92.3% and 73.3% underwent swab testing, respectively. Interestingly, both anosmia (58.3% vs. 41.7%) and dysgeusia (54.5% vs. 45.5%) had only slightly higher frequency in SARS-CoV-2-positive and those who were negative.

Figure 1 compares the daily number of tested subjects along with the number of confirmed cases in the overall population of Modena province, and

Table 2. Clinical signs and symptoms of children and adolescents from Modena province during the first wave from February 24 to June 18, 2020. Data are number (n) and percentage (%) for total population (n=1230), and divided into tested (n=349) and not tested (n=881) subjects.

Clinical signs and symptoms	All subjects (n=1230) n (%)	Tested (n=349) n (%)	Not tested (n=881) n (%)
Fever	106 (8.6)	72 (20.6)	34 (3.9)
Sore throat	30 (2.4)	25 (7.2)	5 (0.6)
Cough	81 (6.6)	61 (17.5)	20 (2.3)
Diarrhea	16 (1.3)	11 (3.2)	5 (0.6)
Vomiting	7 (0.6)	6 (1.7)	1 (0.1)
Headache	40 (3.3)	34 (9.7)	6 (0.7)
Conjunctivitis	8 (0.7)	7 (2.0)	1 (0.1)
Rhinorrhea	51 (4.2)	33 (9.5)	18 (2.0)
Anosmia	13 (1.1)	12 (3.4)	1 (0.1)
Dysgeusia	15 (1.2)	11 (3.2)	4 (0.5)
Asthenia	11 (0.9)	7 (2.0)	4 (0.5)
Respiratory distress	6 (0.5)	6 (1.7)	0 (0.0)

Table 3. Socio-demographic characteristics of children and adolescents tested for SARS-CoV-2, from Modena province during the first wave from February 24 to June 18, 2020 (n=349). Data are number (n) and percentage (%) if not differently reported.

Characteristics	Positive swabs n (%)	Negative swabs n (%)
Overall	78 (22.3)	271 (77.7)
Age[†]	10.0 ± 5.4	9.4 ± 5.2
<6 years	18 (23.1)	81 (29.9)
6-13 years	35 (44.9)	112 (41.3)
≥14 years	25 (32.0)	78 (28.8)
Sex		
Male	33 (42.3)	141 (52.0)
Female	45 (57.7)	130 (48)
Isolation/quarantine place		
Home	72 (92.3)	269 (99.2)
Hospital	4 (5.1)	1 (0.4)
Hotel	2 (2.6)	0 (0.0)
Residential community	0 (0.0)	1 (0.4)
Contagion source		
Cohabiting	61 (78.2)	235 (86.7)
Non-cohabiting	17 (21.8)	36 (13.3)
Contagion context		
Cohabiting relative	61 (78.2)	233 (86.0)
Non-cohabiting relative	6 (7.7)	22 (8.1)
Recreational context	2 (2.6)	3 (1.1)
Health facility visits	0 (0.0)	1 (0.4)
School attendance	0 (0.0)	0 (0.0)
Flight	0 (0.0)	4 (1.5)
Other cohabiting subjects	0 (0.0)	2 (0.7)
Travelling from high-risk areas	0 (0.0)	0 (0.0)
Not reported	9 (11.5)	6 (2.2)
Symptoms		
Yes	61 (78.2)	97 (35.8)
No	17 (21.8)	174 (64.2)
Admitted to hospital		
Yes	6 (7.7)	3 (1.1)
No	72 (92.3)	268 (98.9)
Number of siblings		
0	24 (30.8)	56 (20.7)
1	34 (43.6)	121 (44.6)
2	14 (17.9)	45 (16.6)
3	5 (6.4)	13 (4.8)
≥4	0 (0.0)	20 (7.4)
Not reported	1 (1.3)	16 (5.9)

Characteristics	Positive swabs n (%)	Negative swabs n (%)
Positive cohabitants		
0	3 (3.8)	22 (8.1)
1	11 (14.1)	165 (60.9)
2	12 (15.4)	42 (15.5)
3	18 (23.1)	16 (5.9)
4	13 (16.7)	8 (3.0)
≥5	11 (14.1)	4 (1.5)
Not reported	10 (12.8)	14 (5.2)
Index case removal		
Yes	4 (5.1)	35 (12.9)
No	74 (94.9)	236 (87.1)

†*Mean ± standard deviation*

Table 4. Clinical signs or symptoms of children and adolescents tested for SARS-CoV-2 from Modena province during the first wave from February 24 to June 18, 2020. Data are number (n) and percentage (%) according to subjects with positive (n=78), negative swabs (n=271).

Clinical signs or symptoms	Positive swabs (n=78) n (%)	Negative swabs (n=271) n (%)
Fever	38 (48.7)	34 (12.6)
Sore throat	12 (15.4)	13 (4.8)
Cough	23 (29.5)	38 (14.0)
Diarrhea	6 (7.7)	5 (1.9)
Vomiting	2 (2.6)	4 (1.5)
Headache	15 (19.2)	19 (7.0)
Conjunctivitis	2 (2.6)	5 (1.9)
Rhinorrhea	8 (10.3)	25 (9.2)
Anosmia	7 (9.0)	5 (1.9)
Dysgeusia	6 (7.7)	5 (1.9)
Asthenia	4 (5.1)	3 (1.1)
Respiratory distress	3 (3.8)	3 (1.1)

shows that in the early phase of first wave non-adult subjects were tested for SARS-CoV-2 less frequently than adults.

Similarly, we compared the daily number of RT-PCR tested subjects with the number of confirmed SARS-CoV-2 cases and subjects with symptoms in the pediatric population of Modena province (Figure 2). The number of pediatric swab testing rapidly increased from the beginning of May, 2020, without an increase of the confirmed cases or symptomatic subjects.

Discussion

This study aims to investigate the characteristics among children and adolescent during the first wave of the COVID-19 pandemic in a province of Northern Italy. According to previous findings, the results of our research confirm that during the first wave, characterized by a tight lockdown, the transmission of SARS-CoV-2 occurred through household exposure (28,40), especially in non-adult population as 85.9% of infected children had a positive relative. Interestingly,
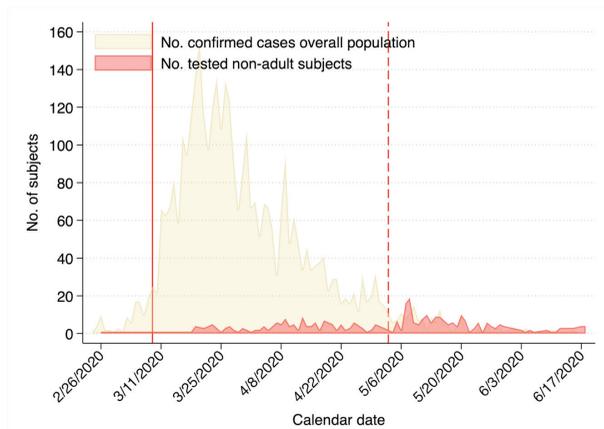
Figure 1. The daily number of tested non adult subjects and the number of confirmed cases in the overall population of Modena province during the first wave from February 24 to June 18, 2020. Solid and dashed lines indicate the begin (March 9, 2021) and end (May 3, 2021) of tight lockdown period, respectively.

Figure 2. The daily number of tested subjects, the number of confirmed cases and subjects with symptoms in the pediatric population of Modena province during the first wave from February 24 to June 18, 2020. Solid and dashed lines indicate the begin (March 9, 2021) and end (May 3, 2021) of tight lockdown period, respectively.

approximately three out of five children with positive swab test had three or more infected cohabitants. This highlights the importance of proper isolation and physical distancing, also during home quarantine, in order to avoid the risk of infection (46).

Based on epidemiological investigation, school contact was recorded in 17 (1.4%) individuals only. However, it is important to underline that in Italy schools were closed at the beginning of March 2020, and have been locked for the remaining study period (47). As a consequence, during the first wave the prolonged closure of schools does not seem to have played a relevant role on the spread of the pandemic according to available data (48), while it has been associated with greater stress and discomfort for children and adolescents (49). Our findings are similar with other studies that suggested a low transmission in schools measuring incidence in school-aged children and adolescents before and during school closures (50,51). Interestingly, a study carried out in Reggio Emilia (a province close to Modena within the same Emilia-Romagna region) reported similar results in terms of transmission in preschools and elementary schools, but not in secondary schools (52). Overall, our results suggest a limited role of children in virus spread during the first wave, in line with other studies (32,53). Conversely during the second wave, an increased risk
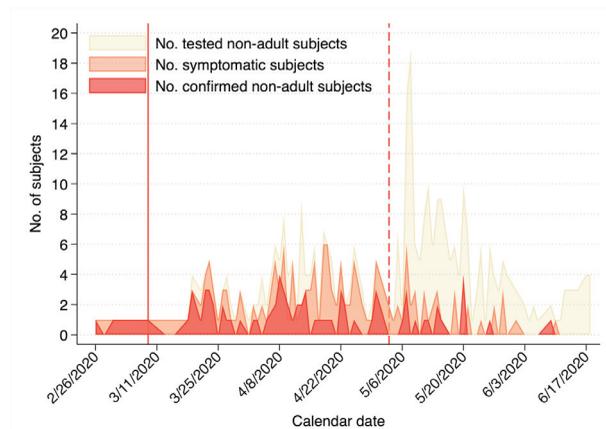
of reported SARS-CoV-2 infection and COVID-19 outcomes was reported among adults living with children, although this was not followed by an increased mortality (54).

Comparing characteristics from tested group with not tested groups, testing strategies have privileged the presence of predictive or risk factors such as: being symptomatic (especially fever, cough and headache), having more than one brother or sister, having more than two positive cohabitants, and hospitalization. About this latter, however, it should be noted that the data about swab testing in hospitalized children are related to routine screening plans set-up for all subjects before admission to emergency room or hospital.

In our study population, the prevalence of confirmed pediatric cases that were asymptomatic is 21.8%, similar to a previous study (55). The clinical presentation in non-adult population with SARS-CoV-2 includes different possible scenarios characterized by a high variation of severity (56). Our findings indicate that subjects with a positive swab reported mostly fever (48.7%), cough (29.5%), headache (19.2%), sore throat (15.4%) and rhinorrhea (15.4%), overall demonstrating a major involvement of respiratory system among children and adolescents. Nevertheless, during the study period, the recommendations on

SARS-CoV-2 case identification indicated RT-PCR testing only for selected non-adult subjects, such as symptomatic or frail individuals in contact with confirmed or highly suspicious cases. As a matter of that, main reasons for RT-PCR testing were if the subject was the first suspicious case within the family or was the contact of confirmed or highly suspicious cases while attended communities or cohabited with frail people people. As a consequence, the prevalence of other presentations (e.g., gastrointestinal, neurological and cutaneous) may have been underestimated in this study, as well as in other studies (17). Interestingly, in contrast with what observed in literature (17), specific clinical features such as anosmia and dysgeusia show only marginal difference between the SARS-CoV-2 positive and negative individuals, suggesting that these symptoms might have a minor pathognomonic role in pediatric population.

The low number of tested children can be explained by the observation that pediatric individuals are more likely asymptomatic or show milder symptoms, therefore, they may have been less often tested or received a positive results as shown in other studies (29,30,32,35), thus affecting the prevalence of positive cases compared to the overall population (36). At the beginning of pandemic, most countries including Italy have chosen to test only symptomatic patients due to the limited availability of swab tests (16). Also international recommendations (16) underline that testing strategies must be adapted in order to ensure an optimal use of resources and alleviate pressure on laboratories. In order to save resources, in early stages of the COVID-19 pandemic, the indication was to de-prioritize testing of mildly symptomatic patients or patients who were not in risk groups (16). Furthermore, after the first positive case in a closed setting (e.g., cluster among workers or relatives), all other individuals with symptoms related to the same cluster may be considered probable cases and quarantined without additional testing, especially when testing capacity was limited (44). According to these recommendations and to our results, during the first pandemic wave, a small number of children has been tested because they were mostly asymptomatic and therefore they were just quarantined at home without additional investigation. This inherently limits the external validity of our findings and related considerations, since only a systematic population-based testing could allow a complete epidemiologic picture of the viral spread in a community, including children (57).

The number of pediatric swab testing rapidly increased when the lockdown started to ease at the beginning of May 2020. The possible reasons might be that, after the lockdown and the decrease of positive cases, more resources were available to test mild and asymptomatic individuals, leading to an increase in tested children and adolescents. In addition, the increased sources of exposure to the infection as a consequence of resume social interactions, including school attendance for children, explain why the number of tests strongly increased after the first wave (5).

In Italy and in general in other countries, increased testing has contributed to a better detection of ongoing transmission (36). In early phases of the COVID-19 pandemic, pediatric cases may have been undetected or underestimated. However, our data (Figure 2) show that in the first weeks after the reopening, compared with the lockdown period, the pediatric case distribution was similar. This can suggest that, in order to save limited testing resources, prioritize symptomatic patients has been a proper strategy.

This study is limited by the number of swab tests (RT-PCR) for SARS-CoV-2 infection due to the shortage of resources. Indeed, serological assays that detect antibodies anti-SARS-CoV-2 were used as support of swab tests in various settings, especially in workplaces (58), despite they had limited diagnostic application in early stages of the pandemic, being especially helpful to better understand the extent of the infection in the community (59). Another limit of our investigations is that we could not investigate deeply transmissions in education settings and those related to activities and behaviors outside of school, such as using public transportation or recreational activities due to the closures. Nevertheless, also considering the limited evidence available on this topic, our findings expand the knowledge regarding characteristics of non-adult subjects quarantined during the first wave of SARS-CoV-2 pandemic. Some strengths should also be outlined. The epidemiological investigations carried out by the Local Health Authorities were mandatory for all Italian population thank to the efforts

of Public Health Departments since the beginning of the pandemic (60), thus occurrence of selection bias can be ruled out. In addition, the detailed epidemiological investigation of the included subjects allowed us to investigated several determinants associated with isolation and testing in the pediatric population (61). Similarly, the thorough assessment of clinical signs and symptoms provide additional and helpful insights about the clinical presentation of COVID-19 in the pediatric population characterized by different features compared to adults (33).

References

1. Docea AO, Tsatsakis A, Albulescu D, et al. A new threat from an old enemy: Reemergence of coronavirus (Review). Int J Mol Med 2020; 45 (6): 1631-43. https://doi.org/10.3892/ijmm.2020.4555.

2. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382 (13): 1199-207. https://doi.org/10.1056/NEJMoa2001316.

3. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. (Accessed September 7, 2021)

4. CPD - Italian Civil Protection Department. COVID-19 data. https://github.com/pcm-dpc/COVID-19. (Accessed September 7, 2021).

5. Vinceti M, Filippini T, Rothman KJ, et al. SARS-CoV-2 infection incidence during the first and second COVID-19 waves in Italy. Environ Res 2021; 197: 111097. https://doi.org/10.1016/j.envres.2021.111097.

6. Signorelli C, Odone A, Gianfredi V, et al. The spread of COVID-19 in six western metropolitan regions: a false myth on the excess of mortality in Lombardy and the defense of the city of Milan. Acta Biomed 2020; 91 (2): 23-30. https://doi.org/10.23750/abm.v91i2.9600.

7. Vinceti M, Filippini T, Rothman KJ, et al. Lockdown timing and efficacy in controlling COVID-19 using mobile phone tracking. EClinicalMedicine 2020; 25: 100457. https://doi.org/10.1016/j.eclinm.2020.100457.

8. Calina D, Hartung T, Mardare I, et al. COVID-19 pandemic and alcohol consumption: Impacts and interconnections. Toxicol Rep 2021; 8: 529-35. https://doi.org/10.1016/j.toxrep.2021.03.005.

9. Copat C, Cristaldi A, Fiore M, et al. The role of air pollution (PM and NO2) in COVID-19 spread and lethality: A systematic review. Environ Res 2020; 191: 110129. https://doi.org/10.1016/j.envres.2020.110129.

10. Dettori M, Deiana G, Balletto G, et al. Air pollutants and risk of death due to COVID-19 in Italy. Environ Res 2021; 192: 110459. https://doi.org/10.1016/j.envres.2020.110459.

11. Di Castelnuovo A, Bonaccio M, Costanzo S, et al. Common cardiovascular risk factors and in-hospital mortality in 3,894 patients with COVID-19: survival analysis and machine learning-based findings from the multicentre Italian CORIST Study. Nutr Metab Cardiovasc Dis 2020; 30 (11): 1899-913. https://doi.org/10.1016/j.numecd.2020.07.031.

12. Filippini T, Rothman KJ, Cocchio S, et al. Associations between mortality from COVID-19 in two Italian regions and outdoor air pollution as assessed through tropospheric nitrogen dioxide. Sci Total Environ 2021; 760: 143355. https://doi.org/10.1016/j.scitotenv.2020.143355.

13. Filippini T, Rothman KJ, Goffi A, et al. Satellite-detected tropospheric nitrogen dioxide and spread of SARS-CoV-2 infection in Northern Italy. Sci Total Environ 2020; 739: 140278. https://doi.org/10.1016/j.scitotenv.2020.140278.

14. Marques M, Domingo JL. Positive association between outdoor air pollution and the incidence and severity of COVID-19. A review of the recent scientific evidences. Environ Res 2021: 111930. https://doi.org/10.1016/j.envres.2021.111930.

15. Ovsyannikova IG, Haralambieva IH, Crooke SN, et al. The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immunol Rev 2020; 296 (1): 205-19. https://doi.org/10.1111/imr.12897.

16. ECDC. European Centre for Disease Prevention and Control Technical Report: Novel coronavirus (SARS-CoV-2). Discharge criteria for confirmed COVID-19 cases: When is it safe to discharge COVID-19 cases from the hospital or end home isolation? 2020. https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-Discharge-criteria.pdf. (Accessed September 7, 2021)

17. Lazzerini M, Sforzi I, Trapani S, et al. Characteristics and risk factors for SARS-CoV-2 in children tested in the early phase of the pandemic: A cross-sectional study, Italy, 23 February to 24 May 2020. Euro Surveill 2021; 26 (14): 2001248. https://doi.org/10.2807/1560-7917.ES.2021.26.14.2001248.

18. Di Castelnuovo A, Costanzo S, Antinori A, et al. Lopinavir/ritonavir and darunavir/cobicistat in hospitalized COVID-19 patients: Findings from the multicenter Italian CORIST study. Front Med (Lausanne) 2021; 8: 639970. https://doi.org/10.3389/fmed.2021.639970.

19. COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. Eur J Intern Med 2020; 82: 38-47. https://doi.org/10.1016/j.ejim.2020.08.019.

20. Tsatsakis A, Calina D, Falzone L, et al. SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. Food Chem Toxicol 2020; 146: 111769. https://doi.org/10.1016/j.fct.2020.111769.

21. Izzotti A, Fracchia E, Au W, et al. Prevention of COVID-19 infection and related complications by ozonized oils. J Pers Med 2021; 11 (3). https://doi.org/10.3390/jpm11030226.

22. Maestre-Muniz MM, Arias A, Mata-Vazquez E, et al. Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. J Clin Med 2021; 10 (13): 2945. https://doi.org/10.3390/jcm10132945.

23. Salamanna F, Veronesi F, Martini L, et al. Post-COVID-19 syndrome: The persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Front Med (Lausanne) 2021; 8: 653516. https://doi.org/10.3389/fmed.2021.653516.

24. Calina D, Hernández AF, Hartung T, et al. Challenges and scientific prospects of the newest generation of mRNA-based vaccines against SARS-CoV-2. Life 2021; 11 (9): 907. https://doi.org/10.3390/life11090907.

25. Abu-Raddad LJ, Chemaitelly H, Coyle P, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. EClinicalMedicine 2021; 35: 100861. https://doi.org/10.1016/j.eclinm.2021.100861.

26. Callaway E. Could new COVID variants undermine vaccines? Labs scramble to find out. Nature 2021; 589 (7841): 177-8. https://doi.org/10.1038/d41586-021-00031-0.

27. Giorgi Rossi P, Marino M, Formisano D, et al. Characteristics and outcomes of a cohort of COVID-19 patients in the Province of Reggio Emilia, Italy. PLoS One 2020; 15 (8): e0238281. https://doi.org/10.1371/journal.pone.0238281.

28. Choi SH, Kim HW, Kang JM, et al. Epidemiology and clinical features of coronavirus disease 2019 in children. Clin Exp Pediatr 2020; 63 (4): 125-32. https://doi.org/10.3345/cep.2020.00535.

29. Parri N, Magista AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: Early findings from two Italian Pediatric Research Networks. Eur J Pediatr 2020; 179 (8): 1315-23. https://doi.org/10.1007/s00431-020-03683-8.

30. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med 2020; 382 (24): 2302-15. https://doi.org/10.1056/NEJMoa2006100.

31. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135794 pediatric patients tested for severe acute respiratory syndrome coronavirus 2 across the United States. JAMA Pediatr 2021; 175 (2): 176-84. https://doi.org/10.1001/jamapediatrics.2020.5052.

32. Ladhani SN, Amin-Chowdhury Z, Davies HG, et al. COVID-19 in children: Analysis of the first pandemic peak in England. Arch Dis Child 2020; 105 (12): 1180-5. https://doi.org/10.1136/archdischild-2020-320042.

33. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: A multinational, multicentre cohort study. Lancet Child Adolesc Health 2020; 4 (9): 653-61. https://doi.org/10.1016/S2352-4642(20)30177-2.

34. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine 2020; 24: 100433. https://doi.org/10.1016/j.eclinm.2020.100433.

35. Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: A systematic review. Eur J Pediatr 2020; 179 (7): 1029-46. https://doi.org/10.1007/s00431-020-03684-7.

36. Bellino S, Rota MC, Riccardo F, et al. Pediatric COVID-19 cases prelockdown and postlockdown in Italy. Pediatrics 2021; 147 (2): e2020035238. https://doi.org/10.1542/peds.2020-035238.

37. West R, Michie S, Rubin GJ, et al. Applying principles of behaviour change to reduce SARS-CoV-2 transmission. Nat Hum Behav 2020; 4 (5): 451-9. https://doi.org/10.1038/s41562-020-0887-9.

38. DPCM 8 marzo 2020. https://www.gazzettaufficiale.it/eli/id/2020/03/08/20A01522/sg (Accessed September 7, 2021)

39. Paduano S, Marchesi I, Frezza G, et al. COVID-19 in school settings: Webinar aimed at both teachers and educators. Ann Ig 2021; 33 (6): 527-32. https://doi.org/10.7416/ai.2021.2437.

40. Signorelli C, Odone A, Stirparo G, et al. SARS-CoV-2 transmission in the Lombardy Region: the increase of household contagion and its implication for containment measures. Acta Biomed 2020; 91 (4): e2020195. https://doi.org/10.23750/abm.v91i4.10994.

41. Neagu M, Calina D, Docea AO, et al. Back to basics in COVID-19: Antigens and antibodies-Completing the puzzle. J Cell Mol Med 2021; 25 (10): 4523-33. https://doi.org/10.1111/jcmm.16462.

42. ECDC. European Centre for Disease Prevention and Control. Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19 – first update. 2020. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-guidance-discharge-and-ending-isolation-first%20update.pdf. (Accessed September 7, 2021)

43. ISS. Special on COVID-19. Everything you need to know. 2020. https://www.iss.it/web/iss-en/at-home-isolation-quarantine-and-close-contacts. (Accessed September 7, 2021)

44. WHO. Laboratory testing strategy recommendations for COVID-19: Interim guidance, 21 March 2020. https://

apps.who.int/iris/handle/10665/331509 (Accessed September 7, 2021)

45. Modena Statistics. On-line demographic data - Resident population and demographic flows2021. http://www.modenastatistiche.it. (Accessed September 7, 2021)

46. Farsalinos K, Poulas K, Kouretas D, et al. Improved strategies to counter the COVID-19 pandemic: Lockdowns vs. primary and community healthcare. Toxicol Rep 2021; 8: 1-9. https://doi.org/10.1016/j.toxrep.2020.12.001.

47. Odone A, Lugo A, Amerio A, et al. COVID-19 lockdown impact on lifestyle habits of Italian adults. Acta Biomed 2020; 91 (9-S): 87-9. https://doi.org/10.23750/abm.v91i9-S.10122.

48. Berselli N, Filippini T, Paduano S, et al. Seroprevalence of anti-SARS-CoV-2 antibodies in the Northern Italy population before the COVID-19 second wave. Int J Occup Med Environ Health 2022; 35 (1). https://doi.org/10.13075/ijomeh.1896.01826.

49. Esposito S, Marchetti F, Lanari M, et al. COVID-19 management in the pediatric age: Consensus document of the COVID-19 Working Group in Paediatrics of the Emilia-Romagna Region (RE-CO-Ped), Italy. Int J Environ Res Public Health 2021; 18 (8): 3919. https://doi.org/10.3390/ijerph18083919.

50. Ludvigsson JF. Children are unlikely to be the main drivers of the COVID-19 pandemic - A systematic review. Acta Paediatr 2020; 109 (8): 1525-30. https://doi.org/10.1111/apa.15371.

51. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: A systematic review and meta-analysis. JAMA Pediatr 2021; 175 (2): 143-56. https://doi.org/10.1001/jamapediatrics.2020.4573.

52. Larosa E, Djuric O, Cassinadri M, et al. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: A population-based study. Euro Surveill 2020; 25 (49): 2001911. https://doi.org/10.2807/1560-7917.ES.2020.25.49.2001911.

53. Nunziata F, Poeta M, Vassallo E, et al. No spread of SARS-CoV-2 from infected symptomatic children to parents: A prospective cohort study in a controlled hospital setting. Front Pediatr 2021; 9: 720084. https://doi.org/10.3389/fped.2021.720084.

54. Forbes H, Morton CE, Bacon S, et al. Association between living with children and outcomes from COVID-19: OpenSAFELY cohort study of 12 million adults in England. BMJ 2021; 372: n628. https://doi.org/10.1136/bmj.n628.

55. Parri N, Lenge M, Buonsenso D, et al. Children with COVID-19 in Pediatric Emergency Departments in Italy. N Engl J Med 2020; 383 (2): 187-90. https://doi.org/10.1056/NEJMc2007617.

56. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020; 145 (6): e20200702. https://doi.org/10.1542/peds.2020-0702.

57. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature 2020; 584 (7821): 425-9. https://doi.org/10.1038/s41586-020-2488-1.

58. Modenese A, Mazzoli T, Berselli N, et al. Frequency of anti-SARS-CoV-2 antibodies in various occupational sectors in an industrialized area of Northern Italy from May to October 2020. Int J Environ Res Public Health 2021; 18 (15): 7948. https://doi.org/10.3390/ijerph18157948.

59. Reno C, Lenzi J, Golinelli D, et al. SARS-CoV-2/COVID-19 Testing: The Tower of Babel. Acta Biomed 2020; 91 (4): e2020144. https://doi.org/10.23750/abm.v91i4.10911.

60. Signorelli C, Fara GM. COVID-19: Hygiene and Public Health to the front. Acta Biomed 2020; 91 (3-S): 7-8. https://doi.org/10.23750/abm.v91i3-S.9507.

61. Hobbs CV, Martin LM, Kim SS, et al. Factors associated with positive SARS-CoV-2 test results in outpatient health facilities and emergency departments among children and adolescents aged <18 Years - Mississippi, September-November 2020. MMWR Morb Mortal Wkly Rep 2020; 69 (50): 1925-9. https://doi.org/10.15585/mmwr.mm6950e3.

Corresponding author:
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Dr. Tommaso Filippini, MD
Department of Biomedical, Metabolic and Neural Sciences
University of Modena and Reggio Emilia
Via Campi 287
Modena, 41125 Italy
Tel. +39 059 2055466
Fax +39 059 2055483
Email: tommaso.filippini@unimore.it
ORCID: 0000-0003-2100-0344