Open screening of SARS-CoV-2 infections in the pediatric population in Marseille, Southern France

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Key Points:

Question: What is the role of open screening of SARS-CoV-2 infections in the pediatric population?

Findings: In this cohort study we reported the first 302 pediatric SARS-CoV-2-positive patients in Marseille, mainly diagnosed thanks to open screening platform (80%).

Meaning: Open screening through a devoted platform may help to detect asymptomatic pediatric carriers and moderately ill children and adolescents, especially in the context of a familial cluster, to better follow them, confer appropriate council, and allow household lockdown.

Abstract:

We described, in a cohort study, the first 302 pediatric SARS-CoV-2-positive patients in Marseille.

SARS-Cov2 PCR performed on respiratory samples between February 24th and April 15th, 2020 at the University Hospital Institute (UHI) Méditeranée Infection in Marseille have been collected.

Age, sex, underlying conditions and obesity, symptoms and their evolution, hospitalization rate, Pediatric Intensive Care Unit (PICU) admissions, mortality rate, viral load and duration of viral excretion were recorded.

From February 24th to April 15th, 49,197 people were tested by PCR to diagnose SARS-CoV-2. Among tested people, 45,433 (92.3%) were adults >18 years old, and 5,558 were SARS-CoV-2-positive (12.2%; sex ratio = 0.91). A total of 3,764 (7.6%) tested people were <18 years old, and 302 were SARS-CoV-2-positive (8.0%; sex ratio = 0.99; Median age 13 years, range [0 day- 18 years]; no death). The children and adolescents were significantly less

frequently positive than adults (8.0% versus 12.2%, p<0.0001). Eighty percent (242/302) of the SARS-CoV-2-positive children and adolescents were tested thanks to the UHI Méditerranée Infection open screening platform.

Viral excretion was followed in 79/302 children and adolescents (26.2%) in a non-standardized manner. The median duration of nasopharyngeal PCR positivity (time between first and last positive tests) was 2 days (min 1, max 14, mean 3.2), and the median time between first positive and first negative tests was 8 days (min 1, max 16, mean 7.1).

Viral load Ct was analyzed for 250/302 (82.8%) children and adolescents and was 27.4 in median (min 13.1, max 34.9, mean 26.8). The median Ct in the 3979/5558 (71.6%) adults for whom viral load was available was 26.1 (min 10.6, max 34.9, mean 25.9).

Complete clinical data for the 30 days following diagnosis were available for 130/302 children (43.0%). A total of 5/130 (3.8%) children and adolescents had obesity and 32/130 were followed for chronic diseases. Forty-two/130 (32.3%) were asymptomatic and diagnosed in the context of familial cases. For the 88/130 other subjects (67.8%), symptoms were very heterogeneous. Twenty-one/130 (16.2%) were admitted in conventional ward, 1/130 (0.8%) in PICU. All clinically recovered. Household COVID-19 exposure was found in 116/130 cases (89.2%).

Manuscript:

Introduction:

SARS-CoV-2 has spread around the world since December 2019 and is currently pandemic.[1,2] Its person-to-person transmission is mainly driven by respiratory droplets and physical contacts with people, contaminated objects or surfaces.[3,4] Oral-fecal[5,6] and aerosolized transmissions are questionnable.[7] This virus highly contagious virus spreads in the community from adults to adults, but children have been mostly described to be infected from adults in their household.[8-10]

Children seem to be less impacted by the disease burden.[11-29] In the United States,[21] children <18 years old represented 1.7% of 149,082 laboratory-confirmed cases (February 12th-April 2nd) although they represent 22% of the global population of the country. In China, 965/44672 SARS-CoV-2-positive patients (2.2%) were <19 years old (416 <10 years old, 449 10-19 years old).[20] Israel reported 1317 children/8329 SARS-CoV-2-positive people in the state (15.8%) (386 < 10 years old, 931 10-19 years old).[27] Marseille first cohort study reported that the children and adolescents < 18 years old accounted for 20/228 SARS-CoV-2-positive patients (8.7%), (10 < 10 years old, 10 10-18 years old).[25] In Iceland, children represented 10/1221 (0.8%) of the positive patients (0 < 10 years-old, 10 10-18 years old).[26] Finally, in Italy, 505/42049 positive patients (1.2%) were < 20 years old (244 < 10 years old, 261 10-20 years old.[28] Moreover, when infected, children were reported to present less severe symptoms and a better prognosis than adults.[11] The underlying mechanisms explaining these data are currently not established. Several hypotheses are proposed: cross immunity due to infections with common, non-SARS human coronaviruses (OC43, NL63, E229, HKU1); different levels of expression of the angiotensin-converting enzyme 2 receptor conditioning the binding of the

virus to the host cells; immaturity of immunity; differences in microbiota components; or less cardiovascular comorbidities.[23]

In Marseille, Southern France (862,211 inhabitants in 2016), the first COVID-19 cases were diagnosed during late February 2020. University Hospital Institute (UHI) Méditerranée Infection implemented at the end of January SARS-CoV-2 specific PCR assays and was able to test widely people and provide results within hours including through a screening ambulatory platform (Amrane et al.).[31] Approximately 49,000 persons have been tested by PCR until mid-April. We report here the 302 first pediatric patients diagnosed with SARS-CoV-2 in Marseille public hospitals.

Material and Methods:

Results of SARS-CoV2 PCR assays performed on nasopharyngeal ± oropharyngeal swabs or sputum samples among children under 18 years between 2020 February 24th to April 15th have been collected. Viral RNA extraction and SARS-CoV-2 RNA detection were performed as previously described (Colson et al.).[25] Briefly, viral RNA was extracted from the respiratory samples using the EZ1 Virus Mini Kit v2.0 on the EZ1 instrument (Qiagen, Courtaboeuf, France) or the QIAamp Viral RNA Mini Kit (Qiagen, Courtaboeuf, France) on the QIAcube automated nucleic acid purifier (Qiagen). Then, SARS-CoV-2 RNA was detected by a real-time reverse transcription (RT)-PCR assay targeting the envelope protein (E)-encoding gene.[30,31] The number of copies of SARS-CoV-2 was estimated and expressed as Cycle threshold (Ct) values.[25]

SARS-CoV-2-positive children and adolescents under 16 years were followed by the pediatric team by phone calls at days 1, 2, 7, 14 and 30 after the date of the 1st positive sample; clinical visits were planned in case of worrying symptoms, and hospitalization was decided in case of

severe symptoms. Positive adolescents over 16-years-old were followed by the infectious diseases adults' team with a pediatric referral if long course comorbidity.

Age, sex, risk factors including chronic diseases and obesity, symptoms and their evolution, hospitalization's rate, Pediatric Intensive Care Unit (PICU) admissions and mortality were recorded.

All patients were included except if the parent formulated opposition to the use of data. Patients analyzed in a previous study[25] and sampled from the 27th of February until the 14th of March were included as their clinical features had not been described.

Statistical analyses were performed with the XLSTAT tool using the Chi-square test for the comparisons of proportions and using the Mann-Whitney test for the comparison of mean values. The significance threshold considered for p value was 0.05.

We compared clinical data available here with those of the seven studies that previously reported clinical information on more than 25 children and adolescents.[16-19,21,22,29]

The UHI Méditerranée infection ethic committee approved the study under the number 2020-019.

The study was registered under the General Data Protection Regulation number 2020-59.

It adhered to the tenets of the revised Declaration of Helsinki and followed the guidelines strobe.

Results:

From February 24th through April 15th, 76,653 PCR to diagnose SARS-CoV-2 were performed at UHI Méditerranée Infection for 49,197 individuals. Among these patients, 5,861 (11.9%; sex ratio = 0.93) were SARS-CoV-2-positive.

Among tested people, 45,433 (92.3%) were adults >18 years old, of whom 5,558 (12.2%; sex ratio = 0.91) were SARS-CoV-2-positive.

A total of 3,764 (7.7%) tested people were <18 years-old, and 302 (8.0%; sex ratio = 0.99; no death) were SARS-CoV-2-positive, of whom 107 were under 10 years old and 195 were 10-18 years old. Median age of these 302 individuals was 13 years (range, 0 day-17 years). Nine (3.0%) were younger than 1 month, 7 (2.3%) were between 1 and 3 months old, 18 (6.0%) were between 3 and 24 months old, 36 (11.9%) were between 3 and 6 years old, 53 (17.5%) were between 6 and 11 years old, 110 (36.4%) were between 11 and 16 years old, and 69 (22.8%) were between 16 and 18 years old.

The children and adolescent were significantly less frequently positive than adults (8.1% versus 12.2%, $p<0.0001$) (Figure 1).

Eighty percent (242/302) of the SARS-CoV-2-positive children and adolescents were tested thanks to the UHI Méditerranée Infection screening platform, notably based on a proven case in the household or in case of respiratory symptoms, even mild. In addition, 17 (5.6%) were diagnosed after admission in pediatric emergency departments or outpatients' clinics, 6 (2.0%) were diagnosed during their hospitalization for other underlying conditions, and 37 (12.2%) had been tested positive in other hospitals around the city.

Viral excretion was followed in 79/302 children and adolescents (26.2%) in a non-standardized manner. Because patients were not tested daily, we have collected the data of the last positive test and the first negative test (median; range). The median duration of nasopharyngeal PCR positivity (delay between the first and last positive tests) was 2 days

(min 1, max 14, mean 3.2), and the median time between the first positive and first negative tests was 8 days (min 1, max 16, mean 7.1). Viral load was available for 250/302 (82.8%) children and adolescents and was 27.4 Ct in median (min 13.1, max 34.9, mean 26.8). In comparison, the median Ct in 3979/5558 (71.6%) adults for whom viral load was available was 26.1 (min 10.6, max 34.9, mean 25.9) (Figure 2).

Complete clinical data for the 30 day-period following the SARS-CoV-2 diagnosis were available for 130 children or adolescents (43.0%). The results are reported in the Tables 1, 2 and 3. A total of 5/130 (3.8%) children had obesity (Body Mass Index (BMI)-for-age charts > 95° percentile) and 32/130 (24.6%) were followed for chronic diseases (Table 3). Forty-two/130 (32.3%) were asymptomatic and diagnosed in the context of familial cases (Table 1). For the 88/130 other children or adolescents (67.8%), symptoms are detailed in Table 2. Twenty-one/130 (16.2%) were admitted in a conventional ward, one/130 (0.8%) in PICU, and 10/130 (7.7%) were hospitalized following a degradation during the two to seven days after the molecular diagnosis (Table 1). The other children or adolescents were ambulatory followed. All pediatric patients clinically recovered, and none of them died. Household COVID-19 exposure was found in 116/130 cases (89.2%) (16 involved cases diagnosed before the lockdown) (Table 1).

Discussion:

We report here a large cohort of SARS-CoV-2-positive pediatric patients. This is the biggest series in Europe and the third biggest worldwide.[16-23,25-27]

In the present series, SARS-CoV-2 seems to infect children and adolescents less frequently than adults based on our observation of a significantly lower proportion of positive subjects

among those tested (8.0% positivity versus 12.2%; p<0.0001), although this difference was smaller than reported previously.[16-23,25-28]

In addition, COVID-19 was found to be exceptionally severe in this young population compared to studies among adults, which corroborates what is reported in the literature.[16-27]

In the present work, it is worthy to note that 80% of the positive pediatric subjects were diagnosed via the screening platform. This may explain that they represented 5.2% of the positive subjects, which is a higher proportion than previously reported in literature (0.8-1.7%).[17,21,29]

This may suggest that testing only severe symptomatic children (during an emergency department visit or a hospitalization) should underestimate the number of positive children. A more restricted strategy of screening consequently misses opportunities of appropriate council, household lockdown and clinical follow up. Conversely, a screening platform, opened to all people in the community, enhances the number of diagnoses in the population and allows extending the isolation of positive patients, which likely impairs the transmission of the disease.[32]

Our SARS-CoV-2-positive pediatric population was evenly comprised of male and female (sex ratio 0.99). The majority of previous pediatric studies showed a predominance of male (sex ratio 1.28-1.77).[16-22,26,29] Most of them involved hospitalized or severely ill pediatric patients. This overrepresentation of males is corroborated with a higher severity of viral diseases in male in childhood for COVID-19[16-22,26,29] and other viral infections like flu.[33] But a bias should also be discussed, as sex ratio in China in global population is 1.17,[34] which could explain an excessive representation of male in the Chinese studies.[16,18,19]

When regarding the whole population of SARS-CoV-2-positive people tested at UHI Méditerranée Infection in Marseille (adults and children), sex ratio was 0.93 being in favor of

women. Previous studies are very heterogeneous regarding the sex ratio among SARS-CoV-2-positive people (0.92-1.76).[8,13, 15] This may reflect if the study was conducted in the setting of an open screening recruitment[8,13] or in hospitalized or severely ill patients (COVID-19 is more severe in men)[15].

The duration of viral excretion seemed to be shorter than in adults,[25,35] and the viral load was significatively lower than in adults, in contrast to what was reported in a previous study.[36] In an earlier work conducted on far smaller numbers of SARS-CoV-2-positive subjects (228) and children or adolescents (Colson P., et al),[25] mean Ct value at the time of diagnosis did not differ between adults and children and adolescents, but the proportion of low Ct values (<19) was 0% in subjects younger than 18 years and 9% in those older than 18 years. In the present study, the proportion of patients with PCR with a Ct value <19 at the time of diagnosis was significantly lower among children and adolescents than among adults. Moreover, this proportion was 1.3% and 3.9% among children younger than 10 years and among children and adolescents between 10 and 18 years of age.

Most of the 130 children analyzable in our study (more than three-quarters) were asymptomatic (32.3%) or with mild symptoms (50.8%) and did not require hospitalization, while all recovered and none died. These data confirm the good prognosis of COVID-19 in children, as mentioned elsewhere.[11-29] It should be also noticed that a large majority of the COVID-19 positive children have no underlying chronic disease, as in other studies.[17,21] Hospitalization rate was of 16.9%, which is lower than reported in literature,[16,17,21] but it is probably linked to our recruitment mode (open screening).

Almost all the symptoms observed in our study have been already well reported in the previous pediatric studies, but it is noteworthy that anosmia, dysgeusia and cutaneous signs were not evaluated in the published pediatric cohorts.[37-39] Here, anosmia and dysgeusia were

found in more than 15% and 13% of subjects, respectively, and cutaneous or mucosa signs was found in 3.8% of the cases. The description of the detailed COVID-19-associated symptoms will be improved in the following months, since more and more case reports and series will be described.[40]

As for other studies,[16,18,21,22] 89% of children and adolescents in our series had been infected through familial exposure. Household exposure seems to be the main mode of transmission of the disease in children (familial clusters).

Finally, we cannot rule out that a part of true SARS-CoV-2-infected patients have been missed, because of a short duration of viral excretion.[19]

Conclusion:

According to the present series, SARS-CoV-2 seems to infect children and adolescents in a significantly lower proportion when compared to adults (8.0% positivity versus 12.2%, $p<0.0001$). Also, children and adolescent's viral excretion was found to be smaller than for adults ($p=0.015$). Moreover, COVID-19 appeared only exceptionally severe in the young population compared to in adults.

Open screening through a devoted platform may help to detect asymptomatic pediatric carriers and moderately ill children and adolescents, especially in the context of a familial cluster, to better follow them, confer appropriate council, and allow household lockdown.

Contrary to influenza virus and respiratory virus infections,[41,42] children and adolescents do not seem to be a major reservoir and vectors of the SARS-CoV-2, and appear to often contract the virus after a household exposure.[43]

Acknowledgment section

Authors contributions:

AM, DR, BC, PC, AF, PM, JCD designed the study, AM, TM, EB, PM, MM, HTD, LL, PC, BLS collected the data, AM, TM, PC, LL analysed the data, AM, BC, PC, DR, AF, PM wrote the manuscript, MM, HTD, EB, JCD, LL, BLS, TM revised the manuscript.

Collaborators

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Data Access, Responsibility, and Analysis

Dr Aurélie Morand had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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The 10 pediatric patients analyzed in a previous study[25] and sampled from the 27th of February until the 14th of March were included as their clinical features had not been described.

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Figure 1: Total tested patients and total SARS-CoV-2-positive patients in the two groups 1) Adults ≥ 18 years old and 2) Chidren and Adolescents [0-18 years old[

Figure 2: Difference of viral load (Ct) in children and alolescents [0-18 years old[versus adults ≥ 18 years old

Table 1: Demographic, presentation, hospitalization and exposition of the present pediatric cohort compare with studies on more than 25 children and adolescents

	Present study	Lu et al.[18]	Ma et al. (Abstract)[22]	Tagarro et al.[17]	Dong et al. (Confirmed)[19]	CDC COVID-19[21]	Parri et al.[29]	Qiu et al.[16]
Population	130	171	115	41	728	2572	100	36
Age Median Range	11 (0-17)	6.7 (1-15)	No data	3 (0-15)	10	11 (0-17)	3.3 (0-17.5)	8.3 (1-16)
Sex ratio	0.94	1.55	1.40	1.28	1.35	1.30	1.30	1.77
Male	63 (48.5%)	104 (60.8%)	73 (63.5%)	23 (56%)	418 (57.4%)	1408 (57.8%)	57 (57.0%)	23 (63.9%)
Female	67 (51.5%)	67 (39.2%)	42 (36.5%)	18 (44%)	310 (42.6%)	1082 (43.2%)	43 (43.0)	13 (36.1%)
	Symptoms							
Asymptomatic infection	42 (32.3%)	27 (15.8%)	61 (53.0%)	No data	94 (12.9%)	1/291 (0 .3%)	21 (21.0%)	10 (27.8%)
Upper respiratory tract infection	40 (30.8%)	33 (19.3%)	No data	14 (34%)	No data	No data	No data	7 (19.4%)
Pneumonia	2 (1.5%)	111 (64.9%)	No data	13 (31.7%)	No data	No data	9 (9.0%)	19 (52.8%)
Others	46 (35.4%)	No data	No data	No data	No data	78/291 (26.8%)	No data	No data
	Hospitalization							
Yes	22 (16.9%)	No data	No data	25 (60%)	No data	147/745 (19.7%)	67 (67.0%)	36 (100%)
No	107 (82.3%)	No data	No data	16 (40%)	No data	598/745 (80.3%)	33 (33.0%)	0 (0%)
	PICU admission							
Yes	1 (0.8%)	No data	3	4 (10%)	No data	15/745 (2.0%)	1 (1%)	No data
Died	0 (0%)	1(0.6%)	0 (0%)	0 (0%)	1 (0.1%)	3/745 (0.4%)	0 (0%)	0 (0%)
	Exposition							
Household	116/130 (89.2%)	154/171 (90.1%)	105/115(91.3%)	No data	No data	168/184 (91.3%)	45 (45.0%)	32/36 (88.9%)

Table 2: Symptoms at diagnosis in the present pediatric cohort compare to the main studies on more than 25 children and adolescents

	Present study	Lu et al.[18]	Tagarro et al.[17]	CDC COVID-19[21]	Qiu et al.[16]	Parri et al.[29]
Population	130	171	41	291	36	100
Cough	41 (31.5%)	84 (48.5%)	No data	158 (54.3%)	7 (19.4%)	44 (44.0%)
Shortness of breath	6 (4.6%)	No data	No data	39 (13.4%)	No data	11 (11.0%)
Pharyngeal erythema	10 (7.7%)	79 (46.2%)	No data	No data	1 (2.7%)	No data
Fever	36 (27.7%)	71 (41.5%)	11 (26.8%)	163 (56.0%)	4 (11.1%)	54 (100%)
Asthenia	30 (23.1%)	13 (7.6%)	No data	No data	No data	9 (9.0%)
Rhinorrhea	34 (26.2%)	13 (7.6%)	No data	21 (7.2%)	No data	22 (22.0%)
Anosmia	20 (15.4%)	No data	No data	No data	No data	No data
Dysgueusia	17 (13.1%)	No data	No data	No data	No data	No data
Anorexia	5 (3.8%)	No data	No data	No data	No data	No data
Vomiting	5 (3.8%)	11 (6.4%)	2 (4.9%)	31 (10.7%)	No data	10 (10.0%)
Thoracic pain	9 (6.9%)	No data	No data	No data	No data	No data
Nasal congestion	30 (23.1%)	8 (5.3%)	No data	No data	No data	No data
Abdominal pain	6 (4.6%)	No data	No data	17 (5.8%)	No data	4 (4.0%)
Diarrhoae	24 (18.5%)	15 (8.8%)	No data	37 (12.7%)	2 (5.6%)	9 (9.0%)
Myalgia	12 (9.2%)	No data	No data	66 (22.7%)	No data	No data
Sore throat	10 (7.7%)	No data	No data	71 (24.4%)	No data	4 (4.0%)
Otitis	2 (1.5%)	No data	No data	No data	No data	No data
Cutaneous and mucosus signs	5 (3.8%)	No data	No data	No data	No data	3 (3.0%)
Headache	28 (21.5%)	No data	No data	81 (27.8%)	No data	4 (4.0%)

Table 3: Description of the underlying conditions of the present pediatric cohort compare with studies on more than 25 children and adolescents

	Present study	CDC COVID-19[21]	Tagarro et al.[17]	Parri et al.[29]
Total population	130	345	41	100
Obesity	5	No data	No data	No data
Comorbidities (some children had one or more comorbidities)	32 (24.6%)	80 (23.2%)	11 (26.8%)	27 (27.0%)
Chronic lung disease	18 (13.8%)	40 (11.6%)	No data	No data
Asthma	14	No data	No data	No data
Pulmonary cystic adenoid malformation	1	No data	No data	No data
Cystic fibrosis	1	No data	No data	No data
Respiratory insuffisance	2	No data	No data	No data
Cardiovascular disease	4 (3.1%)	25 (7.2%)	No data	No data
Cardiopathy	3	No data	No data	No data
Type I diabete	1	No data	No data	No data
Immunosuppression	6 (4.6%)	10 (2.9%)	No data	No data
Leukemia	1	No data	No data	No data
Glanzmann thrombasthenia	1	No data	No data	No data
Hepatitis graft beacause of biliary tract atresia	1	No data	No data	No data
Nephrotic syndrom	1	No data	No data	No data
Juvenile idiopathic arthritis	2	No data	No data	No data
Others	9	No data	No data	No data
Hirschprung disease	1	No data	No data	No data
Down's syndrome	1	No data	No data	No data
Incontinentia pigmenti	1	No data	No data	No data
Sarcoglycanopathy Beta	1	No data	No data	No data
Periodic illness	1	No data	No data	No data
Epilepsia	1	No data	No data	No data
Allergy	3	No data	No data	No data

Figure 1: Total tested patients and total SARS-CoV-2-positive patients in the two groups 1) Adults ≥ 18 years old and 2) Chidren and Adolescents [0-18 years old[

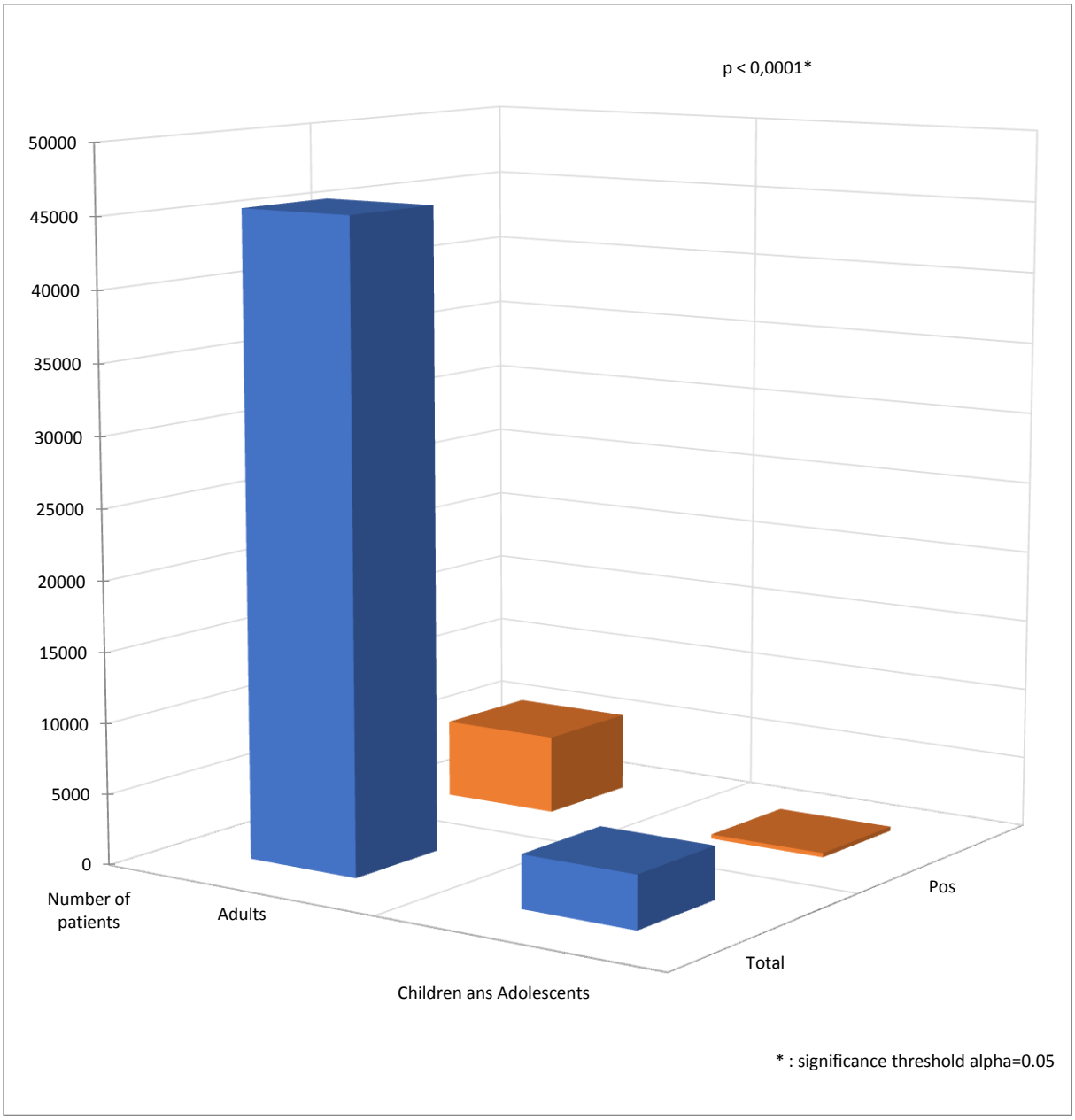

Figure 2: Viral load (Ct) in children and alolescents [0-18 years old[versus adults ≥ 18 years old