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Original article

From the original SARS-CoV-2 strain to the Omicron variant: Predictors of COVID-19 in ambulatory symptomatic children

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ABSTRACT

Objectives: To determine the predictors of a positive SARS-CoV-2 test in a pediatric ambulatory setting.
Patients and methods: We performed a cross-sectional prospective study (November 2020-February 2022) of 93 ambulatory settings in France. We included symptomatic children < 15 years old tested for SARS-CoV-2. For each period corresponding to the spread of the original strain and its variants (period 1: original strain; period 2: Alpha, period 3: Delta; period 4: Omicron), we used a multivariate analysis to estimate adjusted odds ratios (aORs) associated with COVID-19 among age, signs, symptoms or contact, and 95 % confidence intervals (95CIs).
Results: Of 5,336 children, 13.9 % (95CI 13.0–14.8) had a positive test. During the first three periods, the positivity rate ranged from 5.6 % (95CI 4.6–6.7) to 12.6 % (95CI 10.8–14.6). The main factors associated with a positive test were contact with an infected adult at home or outside the home (aOR 11.5 [95CI 4.9–26.9] to 38.9 [95CI 19.3–78.7]) or an infected household child (aOR 15.0 [95CI 4.8–47.1] to 28.4 [95CI 8.7–92.6]). By contrast, during period 4, aORs for these predictors were substantially lower (2.3 [95CI 1.1–4.5] to 5.5 [95CI 3.2–7.7]), but the positivity rate was 45.7 % (95CI 42.3–49.2).
Conclusions: In pediatric ambulatory settings, before the Omicron period, the main predictor of a positive test was contact with an infected person. During the Omicron period, the odds of these predictors were substantially lower while the positivity rate was higher. An accurate diagnostic strategy should only rely on testing and not on age, signs, symptoms or contact.

Introduction

Since the beginning of the COVID-19 pandemic, children developed less severe forms of the disease [1–3]. Furthermore, children — especially younger ones — seemed less susceptible to SARS-CoV-2 infection and less likely to transmit the virus to others [4,5]. However, this situation changed with the spread of the

Abbreviations: COVID-19, Coronavirus disease 2019; IQR, Interquartile range; RAT, Rapid antigen test; RT-PCR, Reverse transcription polymerase chain reaction; SC2-RT-PCR, SARS-CoV-2 reverse transcription polymerase chain reaction; SC-2-RAT, SARS-CoV-2 rapid antigen test.

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Omicron variant. The individual risk of hospitalization for a child infected with the Omicron variant is less, by one-third to one-half, than when the Delta variant was prevalent [6]. However, this lower individual risk was compensated by a striking increase in the incidence of childhood cases leading to unprecedented pediatric hospitalizations in many countries linked in part to the lack of vaccination in children under 12 years of age contrary to adults who had been vaccinated for months [6]. More than 70 % of hospitalized children were under 5 years of age, and most were under 1 year of age; this wave of Omicron hospitalizations has thus particularly affected infants [6]. This situation underlines the importance of considering the variants involved, even in a pediatric study.

Several studies described the clinical signs and symptoms of COVID-19 such as fever, cough, rhinorrhea, digestive signs, and headache in hospitalized children [7,8]. However, these signs and symptoms are commonly shared by many other viral infections that are frequent in childhood and are the main reasons for visits to physicians' offices or pediatric emergency rooms [9]. Thus, clinical signs alone are not sensitive or specific enough for the diagnosis of SARS-CoV-2 infection in children. Moreover, many children, families and practitioners are reluctant to routinely test children with these benign symptoms because their frequency is high in young children and the reliable diagnostic sampling methods are unpleasant and not well accepted by children and their families [10]. Indeed, the nasopharyngeal and/or oropharyngeal swabbing necessary for optimal performance of the SARS-CoV-2 RT-PCR (SC2-RT-PCR) or rapid antigen test (SC2-RAT) can be difficult to perform in ambulatory settings, in children who are not always compliant.

The literature on COVID-19 acute signs and symptoms in ambulatory settings is scarce (hospital emergency departments, ambulatory pediatricians, or family physicians) [11]. A recent study evaluated the clinical presentation and outcomes of children and adolescents who tested positive for SARS-CoV-2 in ambulatory settings, but it took place in the early stage of the pandemic, from March 2020 to November 2020, long before the spread of the Delta and Omicron variants [12].

The aim of the present study was to determine the predictors of a positive SC2-RT-PCR or SC2-RAT result in ambulatory children with symptoms compatible with COVID-19 according to the spread of different variants.

Patients and methods

Study population

From November 2, 2020, to February 15, 2022, the *Association Clinique et Thérapeutique Infantile du Val de Marne* (ACTIV) network conducted a cross-sectional prospective, multicenter study involving 93 centers throughout France, including 13 pediatric emergency department pediatricians and 80 pediatricians in ambulatory settings. Children under the age of 15 years who had COVID-19-compatible symptoms and a SC2-RT-PCR or SC2-RAT result from a nasopharyngeal swab were enrolled in the first few days after symptom onset. Enrollments were nonconsecutive. We excluded patients for whom hospitalization was required or if parents refused participation in the study.

Ambulatory and hospital virology laboratories performed the RT-PCR analysis according to National Reference Center recommendations [13]. The SC2-RAT used was mainly the BIOSYNEX COVID-19 Ag BSS [14].

After informing the parents of participating children of the study, an electronic case report form (eCRF, Supplementary Table 1) was prospectively completed by the pediatrician in a secure database. Any child or parent had the right to object to data collection for the purpose of this study. The following data were prospectively recorded: socio-demographics; day care center/school/college/high school in the last 15 days; contact with a person with confirmed or suspected COVID-19 including details of where the transmission might have occurred (household or outside the household) and age of the index case suspected of having contaminated the child (adult, teenager, or child); symptoms and signs; and results of the SC2-RT-PCR and/or SC2-RAT.

National non-pharmaceutical interventions in France

During the study period, face masks were mandatory at school and day-care center for adults and children > 6 years old. Between October 31, 2020 and December 15, 2020, a non-strict lockdown, without daycare center or school closure, was implemented. Between April 3, 2021 and May 3, 2021, restriction on social life activities were implemented. Daycare centers and schools were closed 1 or 2 weeks in addition to the two-week holyday. Details of non-pharmaceutical intervention implementation are listed by the European Center for Disease Prevention and Control [15]. In addition, school COVID-19 testing programs with salivary tests were conducted but less than 250,000 tests were used in 2021.

French national immunization schedule for SARS-CoV-2 vaccine for children

SARS-CoV-2 vaccination has been recommended since June 15, 2021 for all children older than 12 years. On December 22, 2021, this recommendation was extended to children older than 5 years. By the end of the study in March 2022, vaccine coverage with at least one dose was about 90 % in children aged 12 to 17 years while around 15 % had a complete vaccination schedule (two doses and one booster) [16]. At the same time, 3 % of children aged 5 to 9 years old had received one dose [16].

Test policy in symptomatic children

Guidelines on SARS-CoV-2 testing in symptomatic children were published in September 2020 and did not change over the study period including during the Omicron wave [17]. Since the COVID-19 pandemic, it has been emphasized that all symptomatic children should stay at home. When no other source of fever was identified, testing was immediately recommended for symptomatic children with a confirmed COVID-19 contact and aged $\geq$ 6 years. For younger children with no confirmed COVID-19 contact, testing was recommended when symptoms were severe or lasting for more than 3 days. In our study, COVID-19-compatible symptoms were defined as fever, cough, rhinorrhea, wheezing, dyspnea, dysphagia, diarrhea, vomiting, cutaneous signs, taste loss and/or anosmia, and diffuse pain. Of note, a rapid antigen detection test for the diagnosis of group A *Streptococcus* is recommended in France for all children $\geq$ 3 years old with pharyngitis.

Ethics considerations

Children were included in the study if parents or legal guardians did not object to participation after receiving oral and written information. The study protocol was approved by an ethics committee (Centre Hospitalier Intercommunal de Créteil, France). The study was registered at ClinicalTrials.gov: NCT0441231.

Statistics

We defined four periods according to the lineage of SARS-CoV-2 isolated specimens in France: period 1, when the original strain

was circulating in France (November 2, 2020 to February 14, 2021); period 2, when the Alpha variant was circulating (February 15, 2021 to June 27, 2021); period 3, when the Delta variant was circulating (June 28, 2021 to December 19, 2021); and period 4 when the Omicron variant was circulating (December 20, 2021 to February 15, 2022) [18]. We also analyzed the data according to four age groups: infants and toddlers (1–36 months), pre-school children (3 to 5 years), primary school children (6 to 11 years), and adolescents (12–15 years).

Data were entered using the eCRF (PHP/MySQL) and analyzed with Stata/SE v15 (StataCorp, College Station, TX, USA). Quantitative data were compared using Student's *t* test and categorical data using Chi-square or Fisher's exact test. All tests were 2-sided, and results were considered significant at $p < 0.05$. We used a logistic regression model for analyzing factors associated with a positive SC2-RT-PCR or SC2-RAT result for each period of the study, estimating adjusted odds ratios (aORs) and 95 % confidence intervals (CIs). Among age, daycare attendance for infants and toddlers, COVID-19 confirmed contact (including details of age and location), history of COVID-19 vaccination and/or infection and clinical signs, only factors with p-value < 0.20 on univariate analysis and missing data < 30 % were included in the multivariable model. Data on COVID-19 contact were separated between contact with an adult versus contact with a child, and household contact versus contact outside the home resulting in four different types of confirmed contact. Only significant variables ($p < 0.05$) were kept in the final model.

Results

Between November 2, 2020, and February 15, 2022, we prospectively enrolled 5,336 children presenting symptoms or signs compatible with COVID-19 and who did not require hospital admission: 1,170 in hospital emergency rooms (13 hospitals) and 4,166 in private practice (80 pediatricians). The median age was 3.0 years (interquartile range 1.5–5) and 2,856 (53.5 %) were males. SC2-RT-PCR alone was used for 1,630 (30.6 %) children and SC2-RAT alone for 3,555 (66.6 %); 151 (2.8 %) children had both tests. The proportion of positive test results (SC2-RT-PCR and/or SC2-RAT) over the entire study period was 13.9 % (741/5,336; 95CI 13.0–14.8) and was 5.6 % (102/1,825; 95CI 4.6–6.7) for period 1; 7.4 % (107/1,453; 95CI 6.1–8.8) for period 2; 12.6 % (156/1,236; 95CI 10.8–14.6) for period 3; and 45.7 % (376/822; 95CI 42.3–49.2) for period 4 ($p < 0.001$ between the four periods). During the study period, the proportion of positive tests was higher for SC2-RT-PCR compared to SC2-RAT (302/1,781 or 16.9 % versus 468/3,706 or 12.6 %, $p < 0.001$, Supplementary Table 2).

Fig. 1 presents the positive SC2-RT-PCR and SC2-RAT rate by month according to the presence of confirmed COVID-19 contact and the weekly national incidence and SARS-CoV-2 infection rate described by Public Health France [19]. For the overall study period, the positive test percentage for children with a confirmed COVID-19 contact regardless of its nature was 38.9 % (95CI 36.3–41.6), 7.0-fold higher than for children without a COVID-19 contact (5.6 %, 95CI 4.9–6.3, Chi-square test $p < 0.001$). Irrespective of the period and the non-pharmaceutical intervention, the highest positive test rates were observed with a household contact reported, whether it was a child or an adult. In the pre-Omicron period, the positivity rate was about 20-fold higher for children with a confirmed COVID-19 adult contact in the household than for those without a known contact; by contrast, this difference decreased to 2.4 during the Omicron period (Fig. 1).

Fig. 2 shows the positivity test rate (SC2-RT-PCR and/or SC2-RAT) by age of children and study period. Regardless of the period, children ≤ 12 months and adolescents had a highest positivity rate as compared with other children. In period 4, the highest positivity rates were for children ≤ 12 months and ≥ 73 months.

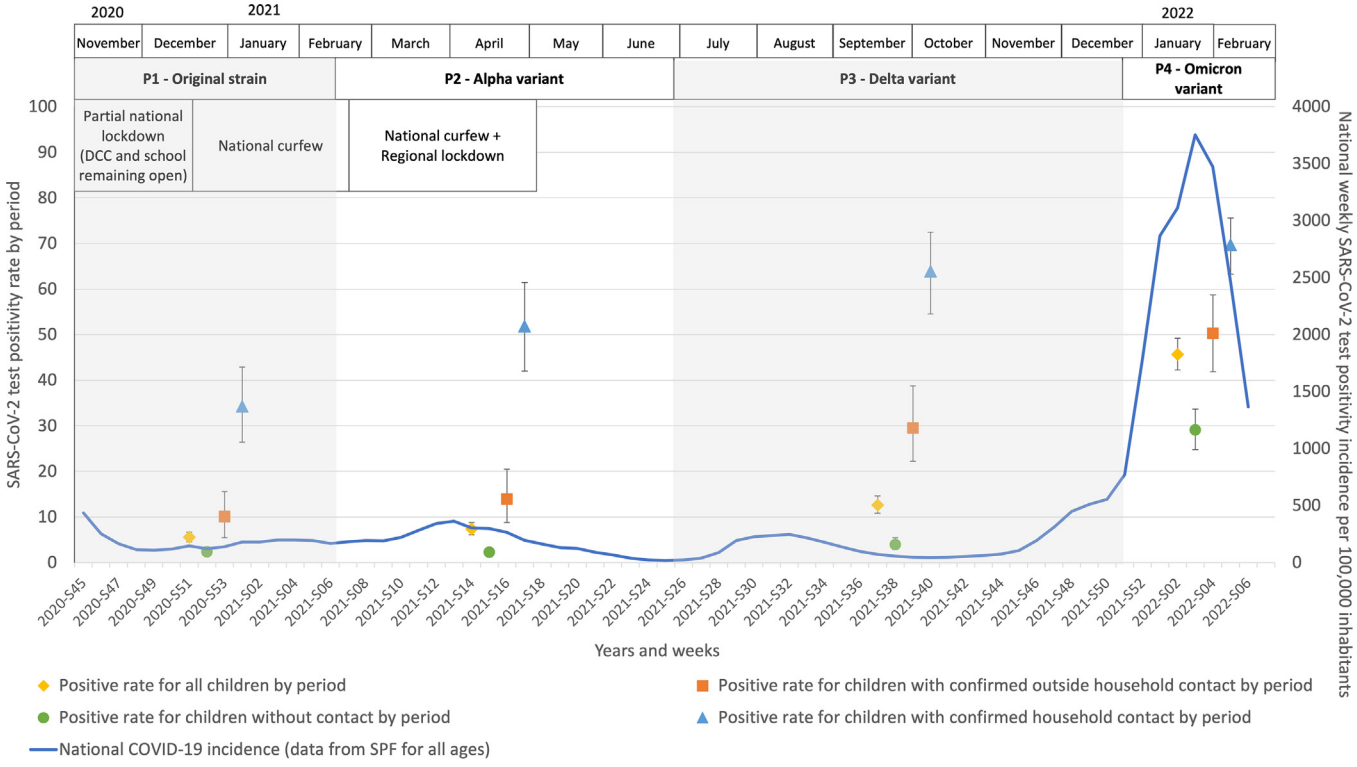


Fig. 1. SARS-CoV-2 test positivity rate (RT-PCR and/or rapid antigen test) according to the presence of confirmed COVID-19 contact for each period. Note: the blue line shows the national incidence described by Public Health France [19]. The periods corresponding to the spread of the original strain and the variants, and the lockdowns/curfew periods are shown. DCC, daycare center; SPF, Santé Publique France (Public Health France).

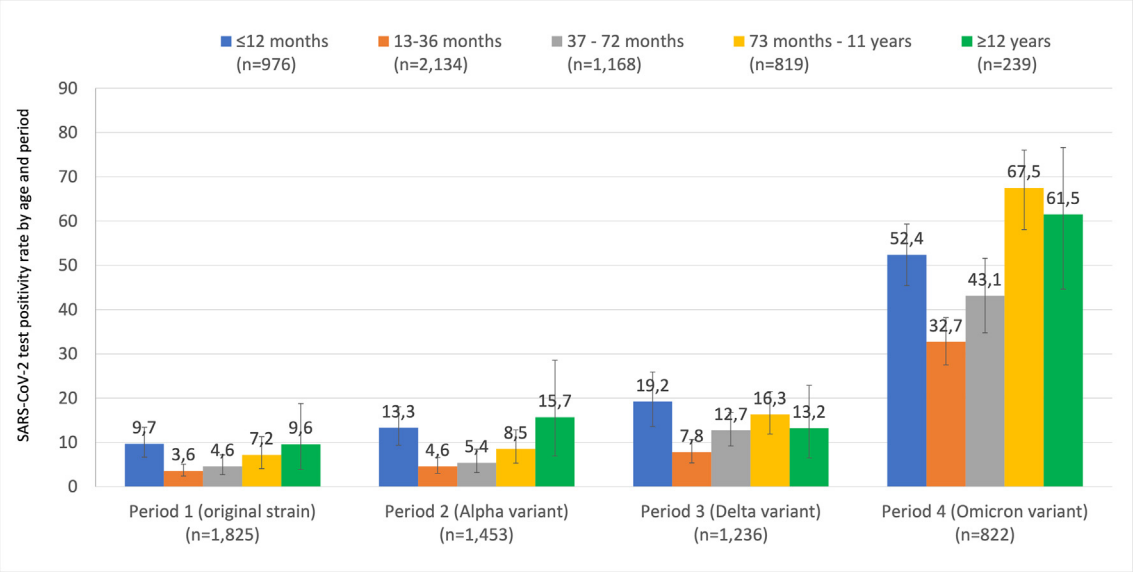


Fig. 2. Distribution of SARS-CoV-2 test positivity rate (RT-PCR and/or rapid antigen test) by age group and period. Data are expressed as mean ± SD.

Table 1 describes the clinical signs and symptoms of children according to the test results and periods. If we consider the overall population or children by periods, many signs and symptoms differed significantly between SARS-CoV-2-infected patients and other patients. As compared with the previous periods, during the Omicron wave, the symptoms seemed to be more marked, with a higher number of cases with fever, chills, and asthenia (Table 2). When comparing children with negative test results by periods, almost all clinical signs significantly varied over time, except for diarrhea (Supplementary Table 3).

The multivariate analysis of predictors of a positive SARS-CoV-2 test result is detailed in Table 3 for each period. The main factors associated with a positive SARS-CoV-2 test were contact with an infected household adult or an adult outside the home (aOR from 2.3 [95CI 1.1–4.5] to 38.9 [95CI 19.3–78.7]) or an infected household child (aOR from 5.5 [95CI 2.8–10.8] to 28.4 [95CI 8.7–92.6]), irrespective of the period. Anosmia/ageusia was the only variable not included in the multivariable model because of 45.3 % of missing data due to the young age of most of the enrolled children (data availability is detailed in Supplementary Table 4). Of note, during the Omicron period, the aOR for these predictors of positive tests were substantially lower than in previous periods.

During the Delta period, the SARS-CoV-2 test positivity rate was 3.0 % (2/67) for children with a history of SARS-CoV-2 vaccination and/or proven COVID-19 versus 13.4 % (151/1,129) for children otherwise (p = 0.008). By contrast, we found no significant difference between these groups during the Omicron period (43.4 % [23/53] vs 45.5 % [348/764], p = 0.78, Supplementary Table 5). Of note, before the Delta variant spread, no child reported a SARS-CoV-2 vaccination nor a history of COVID-19.

Discussion

To our knowledge, the present study is the largest prospective study exclusively devoted to COVID-19 signs and symptoms during the acute disease phase in non-hospitalized children that covers the epidemic waves due to the original strain, and the Alpha, Delta, and Omicron variants [11]. Among the 5,336 children enrolled, 741 had a positive SARS-CoV-2 test result. The rate of positive tests (45.7 %) and the number of infected children (n = 376) was higher during the two-month Omicron period than during the previous three periods (n = 365), representing 13 months, which attests to the high contagiousness of this variant.

During the study period, we observed significant differences between children with a negative SARS-CoV-2 test results and children with a positive test. A higher proportion of children with COVID-19 had chills, anosmia/ageusia, pain, and headache. By contrast, children with a positive test had a lower proportion of rhinorrhea, poor eating, cough, dyspnea/wheezing, vomiting, and diarrhea. However, no clinical signs or symptoms differentiated COVID-19 from other causes in children. Altered taste and smell have been described as specific to COVID-19 and strongly points to the diagnosis, but symptoms were only reported in a few children, and mostly in young adolescents; thus, this data cannot be transposed to primary care pediatric settings [20]. When included in a multivariate analysis with contacts, age, and daycare center/primary school/secondary school/high school attendance, clinical signs and symptoms were poorly associated with a positive test. Dyspnea/wheezing (OR 2.7, 95CI 1.4–5.1), and the absence of sore throat (OR 2.4, 95CI 1.4–4.1) was associated with a positive test during the Delta period, and the absence of cough (1.7, 95CI 1.2–2.4) and diarrhea (2.0, 95CI 1.2–3.1) was associated with a positive test during the Omicron period. These findings highlight the poor specificity of clinical signs and symptoms in children with COVID-19 in ambulatory settings. Furthermore, the comparison was made with SARS-CoV-2-negative symptomatic children whose symptoms are variable according to the other respiratory viruses circulating.

The test positivity rate increased in each period and almost in all age groups reflecting the increased viral circulation due to the higher transmissibility of the Delta variant compared to the ancestral strain [21] and of the Omicron variant compared to Delta [22]. This difference is illustrated by the maximal number of daily positive tests in France: 365,000 during the Omicron period compared to less than 50,000 during the pre-Omicron period [23]. Furthermore, the relative risks of having a positive test decreased sharply during the omicron period reflecting changes in the disease transmission patterns. Regardless of the variant, the main factor predicting SARS-CoV-2 infection was contact with a person with proven COVID-19, particularly a household member (child or adult). However, during the pre-Omicron periods, the risk of a positive test result was multiplied by more than 20 in children with a positive household contact as compared with children with no

Table 1
Distribution of symptoms according to the results of SARS-CoV-2 tests (RT-PCR and/or rapid antigen test [RAT]) by periods.

	Period 1 (Original strain) RT-PCR and/or RAT test		Period 2 (Alpha variant) RT-PCR and/or RAT test		Period 3 (Delta variant) RT-PCR and/or RAT test		Period 4 (Omicron variant) RT-PCR and/or RAT test		Overall RT-PCR and/or RAT test	
	Negative N = 1,723	Positive N = 102	Negative N = 1,346	Positive N = 107	Negative N = 1,080	Positive N = 156	Negative N = 446	Positive N = 376	Negative N = 4,595	Positive N = 741
Age (years), median (IQR)	3 (1.4–5)	2 (0.75–6)	3 (1.5–5)	2 (0.8–7)	4 (2–7)	4 (1.7–8.5)	2 (1.2–4) **p < 0.0001**	3 (0.9–7)	3 (1.5–5) **p < 0.001**	3 (0.9–7)
Male	54.3	51.0	51.0	52.3	55.7	54.5	54.0	52.6	53.6	52.8
Daycare center/primary school/ secondary school/high school in the last 15 days	85.3 **p < 0.0001**	64.4	84.8 **p < 0.0001**	64.1	88.9 **p < 0.0001**	72.9	82.8 **p < 0.0001**	69.2	85.8 **p < 0.0001**	68.6
Fever	81.1	74.2	77.4	71.7	80.7	79.9	85.4	86.4	80.3	81.3
Chills	19.7	18.7	16.6	15.5	19.9	20.9	33.4	30.4	20.2 **p = 0.006**	24.7
Rhinorrhea	66.8	58.5	70.9	69.2	78.7	76.5	76.6 **p = 0.001**	65.9	71.8 **p = 0.02**	67.6
Anosmia/ageusia	2.1	5.8	1.7	1.6	4.4 **p = 0.01**	10.1	0.6 **p = 0.03**	3.9	2.4 **p = 0.001**	5.3
Poor eating	36.7	27.6	42.4	36.1	40.8 **p = 0.008**	29.3	42.9	38	40.1 **p = 0.006**	34.5
Cough	55.6	46.2	62.6	62.7	69.7	66	67 **p=<0.001**	53.4	62.2 **p = 0.005**	56.6
Dyspnea/wheezing	16.7	12.6	19 **p = 0.003**	7.1	13.9 **p = 0.006**	22.8	8	8.5	15.9 **p = 0.008**	11.9
Pain	12.4	11.7	12.8	20	15.9	20.7	19.6	21.9	14 **p < 0.001**	20.1
Asthenia	48.4 **p = 0.03**	36.6	42.9	48.9	51.6	46.7	54.5	54.4	48.1	49.5
Headache	26.6	33.3	22.7 **p = 0.03**	33.8	33.6	39.2	25.5 **p = 0.01**	35.3	27 **p < 0.001**	35.8
Sore throat	34.1 **p = 0.03**	21.7	31.3	33.3	43.9 **p=<0.001**	20.1	26.6	26.4	34.9 **p < 0.001**	25.3
Nausea	14.2	15.4	17.7	10.3	12.5	8.6	11.3	13.6	14.6	12.3
Vomiting	21.3 **p = 0.02**	11.2	23.2	15.2	18.2	15.8	20.7	19.7	21.1 **p = 0.02**	17.1
Diarrhea	18.4	16.5	18.6	20.2	16.9	12.8	19.9 **p = 0.001**	11	18.3 **p = 0.002**	13.4
Cutaneous signs	5	4.5	2.9	6.3	1.8	2.8	4.1	5.1	3.5	4.7

Data are displayed as percentage of available data unless otherwise indicated. Non-significant p-values are not shown (quantitative data were compared by Student's *t* test and categorical data by Chi-square or Fisher's exact test between children with negative and positive SARS-CoV-2 test results during the four periods and the overall study period). Significant p-values (<0.05) are in bold.

Table 2
Distribution of symptoms in children with positive RT-PCR and/or RAT test in the non-Omicron and Omicron periods.

	Non-Omicron period N = 365	Omicron period N = 376	p-values
Age (years), median (IQR)	3 (1–7)	3 (0.9–7)	0.48
Male	52.9	52.7	0.95
Fever	75.9	86.4	**<0.001**
Chills	18.8	30.4	**<0.001**
Rhinorrhea	69.5	65.9	0.30
Anosmia/ageusia	6.6	3.9	0.22
Poor eating	30.8	38	0.05
Cough	59.8	53.4	0.09
Dyspnea/wheezing	15.5	8.5	**0.006**
Pain	18.2	21.9	0.26
Asthenia	44.5	54.4	**0.01**
Headache	36.3	35.3	0.86
Sore throat	24.1	26.4	0.57
Nausea	10.9	13.6	0.33
Vomiting	14.4	19.7	0.07
Diarrhea	15.9	11	0.06
Cutaneous signs	4.3	5.1	0.72

Data are displayed as percentage of available data unless otherwise indicated. Quantitative data were compared by Student's *t* test and categorical data by Chi-square or Fisher's exact test. Significant p-values (<0.05) are in bold.
RAT: rapid antigen test.

known contact, during the Omicron period, this risk was reduced to 2.4. This is an additional argument in favor of the very high contagiousness of the Omicron variant among children [18,24]. The increased transmissibility of the Omicron variant may explain how contacts at school were responsible for contamination despite social distancing. Furthermore, adult protection obtained through vaccination may have decreased the role of contacts in children contamination [25]. By contrast, contact with an infected child outside the home was not a risk factor in period 1, when children were less contagious [26]. As most children included in our study are too young to be vaccinated (median age of 3 years), our findings highlight that they could benefit from indirect protection through parental vaccination [25].

Children with no daycare center/primary school/secondary school/high school attendance in the last 15 days were at higher risk of having a positive SARS-CoV-2 test. This relation was observed during the four periods with OR varying from 2.1 to 4.1. In our study, the median age was 3.0 years (interquartile range 1.5–5), and the collectivity attendance concerned nearly all children older than 3 years for which school attendance is mandatory. Thus, the difference in collectivity attendance was mostly for daycare center attendance. These results are in accordance with low SARS-CoV-2 seroprevalence in children attending daycare centers [27] and the important role of adults in children infection. Several hypotheses could explain these findings. First, children cared at home may be in longer contact with adults at home, which are often the source of contamination. Second, the mandatory wear of face mask for adults working at daycare centers could have protected the children from COVID-19. Third, children in daycare centers may have been protected against SARS-CoV-2 by a better trained innate immunity due to their higher exposure to respiratory viruses [28,29]. Finally, the correlation between the absence of daycare attendance and lower socioeconomic status may be in cause [30] as COVID-19 incidence is higher in adults with lower socioeconomic status [31].

Each variant of SARS-CoV-2 could induce the different signs and symptoms of COVID-19 in children [12]. However, as shown in Tables 2 and 3, the most significant differences were observed between the Omicron period and the other epidemic waves. Indeed, in comparing the different periods, during the Omicron wave chills, fever and asthenia were more frequent, and dyspnea-wheezing (indicating a lower respiratory tract infection) was less frequent. These data confirm those of a recent study from Spain reporting a higher proportion of fever and symptoms of upper respiratory tract infections (such as rhinorrhea or sore throat) during the Omicron wave than in previous waves in children visiting emergency departments [32].

The comparison of symptoms over the 15-month study showed that the symptoms of children with a SARS-CoV-2 negative test significantly varied over the study, which reflects the circulation of other viruses [33–35]. The epidemiology of other respiratory viruses has deeply changed due to the non-pharmaceutical interventions implemented [36,37]. In this context, clinicians could use multiplex PCR and/or antigen combo tests (SARS-CoV-2, respiratory syncytial virus, and influenza) for the diagnosis of respiratory tract infections in ambulatory settings.

In July 2021, France recommended vaccinating all children aged between 12–17 years against SARS-CoV-2, with a high vaccine coverage obtained (about 80 % for two doses) [38]. Here, we found that in period 3, the rate of infected children was significantly lower for COVID-19-vaccinated or previously infected children than for other children. By contrast, during the Omicron wave, which particularly affected children, this difference was not observed. This finding underlines the robustness of our real-life study [39,40]. Indeed, a low protection against the Omicron variant has been reported in adolescents, particularly against non-critical COVID-19 as in our study [41].

This study has several limitations. First, we cannot exclude that some differences among periods could be related to changes in testing policy by physicians and in seeking medical attention by parents over time. Several factors such as availability of tests, national information on epidemic waves, and experience of clinicians may have changed over the long study period. Furthermore, medical seeking behaviors may have varied after multiple COVID-19 waves, particularly in parents with a positive COVID-19 test and ill children. Parents may have avoided testing for their children with milder symptoms to avoid home isolation, particularly for children attending daycare center. During the Omicron period, a new article, available for both parents and physicians, reported that children were at high risk of COVID-19 [6]. It is important to note that the national guidelines on SARS-CoV-2 testing in children were published in September 2020 and did not change over the study period [17]. Furthermore, the use of multivariate analysis reduces bias that could be induced by differences of children in the various time periods. Second, we mainly used SC2-RAT for the diagnosis of infection. Antigen tests are less sensitive than RT-PCR, but all children in our study had samples taken within the first 4 or 5 days of symptom onset when the viral load and sensitivity of antigen tests were optimal [42]. We observed a higher proportion of positive tests when RT-PCR was used compared to RAT suggesting that clinicians tend to use these tests differently, although neither the guidelines nor the protocol of this study made a distinction between these tests. Third, we did not include asymptomatic patients to determine whether the presence of symptoms increased the risk of a positive result. Therefore, we were not able to determine whether sampling symptomatic children is more contributive than routine sampling of asymptomatic children in some settings. We did not include severe patients requiring hospitalization, who may have different clinical signs and symptoms. The third limitation is that we did not search for the other causes of respiratory tract infections (particularly a search for other viruses by multiplex PCR). Therefore, we were not able to determine the causes of the infections in SARS-CoV-2-negative symptomatic children nor the possible role of co-infections. Finally, we cannot exclude that other factors, such as family gathering during

Table 3
Multivariate analysis of predictors of a positive SC2-RT-PCR and/or rapid antigen test result for each period.

	Period 1 (original strain) N = 1,825			Period 2 (Alpha variant) N = 1,453			Period 3 (Delta variant) N = 1,236			Period 4 (Omicron variant) N = 822		
	n/N (%)	aOR (95CI)	p-value	n/N (%)	aOR (95CI)	p-value	n/N (%)	aOR (95CI)	p-value	n/N (%)	aOR (95CI)	p-value
Contact												
None	1,559/1,825 (85.4)	1		1,194/1,453 (82.2)	1		172/1,236 (13.9)	1		451/822 (54.9)	1	
Confirmed contact with an infected household adult	120/1,825 (6.6)	18.5 (11.2–30.7)	**<0.001**	93/1,453 (6.4)	33.7 (17.8–63.9)	**<0.001**	426/1,236 (34.5)	38.9 (19.3–78.7)	**<0.001**	163/822 (19.8)	5.0 (3.2–7.7)	**<0.001**
Confirmed contact with an infected household child	17/1,825 (0.9)	15.0 (4.8–47.1)	**<0.001**	15/1,453 (1.0)	28.4 (8.7–92.6)	**<0.001**	316/1,236 (25.6)	15.1 (5.5–41.7)	**<0.001**	65/822 (7.9)	5.5 (2.8–10.8)	**<0.001**
Confirmed contact with an infected adult outside the home	48/1,825 (2.6)	13.2 (6.1–28.8)	**<0.001**	57/1,453 (3.9)	11.5 (4.9–26.9)	**<0.001**	246/1,236 (19.9)	15.3 (5.5–42.2)	**<0.001**	40/822 (4.9)	2.3 (1.1–4.5)	**0.02**
Confirmed contact with an infected child outside the home	81/1,825 (4.5)	1 (0.2–4.4)	0.98	94/1,453 (6.5)	4.2 (1.9–9.4)	**<0.001**	76/1,236 (6.1)	6.8 (3.5–12.9)	**<0.001**	103/822 (12.5)	2.1 (1.3–3.4)	**0.004**
Age group												
≤12 months	333/1,825 (18.1)	1		263/1,453 (18.1)	1		172/1,236 (13.9)	1		210/822 (25.6)	1	
13–36 months	805/1,825 (44.1)	0.6 (0.3–1.0)	0.05	588/1,453 (40.5)	0.4 (0.2–0.9)	**0.03**	426/1,236 (34.5)	0.8 (0.3–2.2)	0.73	315/822 (38.3)	0.7 (0.5–1.1)	0.17
37–72 months	392/1,825 (21.5)	1 (0.5–2.0)	0.94	316/1,453 (21.8)	0.8 (0.4–2.0)	0.69	316/1,236 (25.6)	3 (1.1–8.1)	**0.03**	144/822 (17.5)	1.2 (0.7–2.1)	0.52
73 months–11 years	224/1,825 (12.3)	1.5 (0.7–3.4)	0.28	235/1,453 (16.2)	1.5 (0.6–3.4)	0.36	246/1,236 (19.9)	5.8 (2.1–16.1)	**0.001**	114/822 (13.9)	3.6 (2–6.6)	**<0.001**
≥12 years	73/1,825 (4.0)	1.9 (0.7–5.3)	0.23	51/1,453 (3.5)	2.8 (0.9–8.5)	0.07	76/1,236 (6.1)	5.2 (1.5–18.1)	**0.009**	39/822 (4.7)	2.9 (1.3–6.5)	**0.009**
Daycare center/primary school/secondary school/high school in the last 15 days												
Yes	1,488/1,770 (84.1)	1		1,127/1,354 (83.3)	1		1,068/1,229 (86.9)	1		624/815 (76.6)	1	
No	282/1,770 (15.9)	3.5 (2.0–6.2)	**<0.001**	227/1,354 (16.7)	2.1 (1.1–4)	**0.03**	161/1,229 (13.1)	4.1 (2.0–8.4)	**<0.001**	191/815 (23.4)	2.1 (1.4–3.3)	**0.001**
Dyspnea/wheezing												
Yes				1,091/1,332 (18.1)	1		171/1,135 (15.1)	2.7 (1.4–5.1)	**0.003**			
No				241/1,332 (81.9)	2.6 (1.0–7.1)	0.05	964/1,135 (84.9)	1				
Sore throat												
Yes							399/981 (40.7)	1				
No							582/981 (59.3)	2.4 (1.4–4.1)	**0.001**			
Cough												
Yes										482/793 (60.8)	1	
No										311/793 (39.2)	1.7 (1.2–2.4)	**0.002**
Diarrhea												
Yes										120/763 (15.7)	1	
No										643/763 (84.3)	2.0 (1.2–3.1)	**0.005**

aOR, adjusted odds ratio; 95CI, 95 % confidence interval.
Significant p-values (<0.05) are in bold.

Christmas holiday at the beginning of the Omicron wave or indirect protection of children through parental vaccination [25], changed the mode of transmission.

Conclusion

This large prospective study of predictors of a SARS-CoV-2-positive test result in non-hospitalized children highlights the need to differentiate two periods. During the pre-Omicron period, the main factor predicting SARS-CoV-2 infection was contact with a person with proven COVID-19, particularly a household member (adult or child), rather than clinical signs, symptoms or age group. During the Omicron period, the odds of these predictors was substantially lower than in previous periods and the overall proportion of positive test results was higher (about 1 in 2). In this context, we confirm that an accurate diagnostic strategy should only rely on laboratory testing and not on signs, symptoms or contact.

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Availability of data

Data are available upon reasonable request.

Ethics considerations

Children were included in the study if parents or legal guardians did not object to participation after receiving oral and written information. The study protocol was approved by an ethics committee (Centre Hospitalier Intercommunal de Créteil, France). The study was registered at ClinicalTrials.gov: NCT0441231.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RC received personal fees and non-financial support from Pfizer outside the submitted work and personal fees from AstraZeneca, GSK, Merck, and Sanofi outside the submitted work. AR reports travel grants from Pfizer and AstraZeneca outside the submitted work. NO reports travel grants from Pfizer, GSK and Sanofi outside the submitted work. FA reports travel grants from Pfizer outside the submitted work. CL received personal fees and non-financial support from Pfizer outside the submitted work. All other authors declare no competing interests for this study.

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Authors' contributions

RC, CL designed the study. RC, CL, AR, and SB analyzed and interpreted the data and drafted the article. RC, CL, and SB performed the statistical analysis. All authors revised and approved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idnow.2022.09.012.

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