Original article

Prospective evaluation of the point-of-care use of a rapid antigenic SARS-CoV-2 immunochromatographic test in a paediatric emergency department

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ABSTRACT

Objectives: This study aimed to evaluate the immunochromatographic coronavirus disease 2019 (COVID-19) speed antigen test (BioSpeedia, France) as an antigen point-of-care test (AgPOCT) to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at the paediatric emergency department of the University Hospital of Saint-Etienne in France.
Methods: Between 15 January and 28 May, 2021, children presenting with respiratory symptoms compatible with COVID-19 infection (symptomatic group) or those requiring hospitalization for any reason (asymptomatic group) were included prospectively and received a nasopharyngeal aspiration to carry out both AgPOCT and quantitative reverse transcription (RT) PCR (RT-qPCR) tests, with the latter being used as the reference standard, for the diagnosis of SARS-CoV-2 infection.
Results: Among the 1009 enrolled children, we obtained a result from both techniques for 990: 33 (3.3%) tested positive with AgPOCT and 46 (4.6%) with RT-qPCR. The overall sensitivity and specificity of the AgPOCT were 69.6% (95% confidence interval (CI), 54.3–82.3) and 99.9% (95% CI, 99.4–100), respectively, compared with the RT-qPCR. Sensitivity increased to 82.9% (95% CI, 66.4–93.4) in symptomatic children. The mean cycle threshold value was significantly lower in positive samples for AgPOCT than in negative samples in the overall population and in both the symptomatic and asymptomatic groups.
Discussion: The use of the COVID-19 speed antigen test at the bedside in the emergency department has satisfactory performance for diagnosing SARS-CoV-2 infection in symptomatic children. **Quentin Ollier, Clin Microbiol Infect 2022;28:734.e1–734.e6**
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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan, China, causing the ongoing coronavirus disease 2019 (COVID-19) pandemic. Virus detection has been widely recommended to undertake interventions based on case findings and contact tracing. In symptomatic patients, spread of the infectious virus primarily occurs before symptom onset. Quantitative reverse transcription PCR (RT-qPCR) testing performed on a nasopharyngeal sample is the reference standard for SARS-CoV-2 detection [1]; it allows for a semiquantitative estimation of viral load by the cycle threshold (Ct) value. Nevertheless, this kind of molecular assay requires trained personnel, sophisticated laboratory equipment, and logistical planning. The assays are not fully adapted to the rapid screening of patients infected with SARS-CoV-2 who present to the emergency department [2]. Consequently, delays in obtaining RT-qPCR results can rarely be shortened and can even be slowed down by the increasing

demand for tests [3], whereas quickness of results is a crucial factor to control viral transmission.

By mid-2020, in parallel with rapid molecular tests based on different amplification technologies (e.g. loop-mediated isothermal amplification or RT-PCR), antigen point-of-care tests (AgPOCT) appeared as an exciting and cost-effective alternative for rapid SARS-CoV-2 diagnosis. Although their analytical performance is inferior to that of RT-qPCR [4], they allow for bedside testing, giving a piece of essential information within a few minutes. Despite the availability of myriad commercial SARS-CoV-2 AgPOCT, each has to be carefully evaluated in field conditions. Several evaluations of antigen tests have been published, but most of these studies were conducted either in adults only [4–8] or in both adults and children [9,10]. This can be explained by the fact that children are considered far less important drivers of COVID-19 infection than adults [11–13]. Nevertheless, children can be part of the transmission chain [14], as evidenced by the increasing number of positive tests in the student population since the reopening of schools around the world. To the best of our knowledge, the accuracy of only two commercial AgPOCT kits has been evaluated in the paediatric population [15–17].

The objective of the present study was to evaluate the performance of the COVID-19 speed antigen test (BioSpeedia) prospectively as an AgPOCT for the diagnosis of SARS-CoV-2 infection in nasopharyngeal samples compared with an RT-qPCR assay in children with rapid tests performed directly in the paediatric emergency department.

Methods

This is a single-centre, prospective study performed at the University Hospital of Saint-Etienne in Saint-Etienne, Loire Department, France, from 15 January to 28 May, 2021. The COVID-19 speed antigen test was chosen for its excellent performance in the adult population at our hospital (unpublished data).

Inclusion and exclusion criteria

Patients between 0 and 15 years old and those older who had still regular paediatric follow-ups were eligible. Each child for whom an AgPOCT test was performed was included prospectively. The indication to perform a test at our centre was the presence of symptoms indicative of COVID-19 infection, potential contact with an infected person, and/or hospitalization. Institutionally, each hospitalized child was systematically tested for SARS-CoV-2 infection before entering the hospital ward, whatever the reason for hospitalization.

Two categories of patients were defined retrospectively. The symptomatic group included all patients presenting a clinical picture compatible with COVID-19 infection, as described for children by Mansourian et al. [18], including fever, cough, vomiting, diarrhoea, sore throat, and dyspnoea. The asymptomatic group included all other patients whose symptoms were not considered clinically indicative of COVID-19 infection. The data collected at the time of enrolment are shown in Table 1.

Procedures

According to the current procedure of the paediatric emergency department [19], a single nasopharyngeal aspirate (NPA) was performed for each child by a nurse using an atraumatic flexible hose. After NPA sampling, the sterile swab provided in the AgPOCT kit was immersed in the sample and rolled three times before being introduced into the reagent tube. The AgPOCT was then performed

Table 1
Demographics and main clinical characteristics of study participants

Characteristics	Overall (N = 1009)	Symptomatic (n = 493)	Asymptomatic (n = 516)	p-value
Age (y), mean (SD)	3.7 (4.4)	2.3 (3.1)	5.0 (5.0)	<0.001
Age category (y), n (%)				<0.001
<2	551 (54.6)	328 (66.5)	223 (43.2)	
2−10	323 (32.0)	142 (28.8)	181 (35.1)	
11−15	116 (11.5)	22 (4.5)	94 (18.2)	
>15	19 (1.9)	1 (0.2)	18 (3.5)	
Male sex, n (%)	547 (54.3)	269 (54.6)	278 (53.9)	0.88
Gravity rank at admission, n (%)				0.40
1 (the most serious health condition)	19 (1.9)	9 (1.8)	10 (1.9)	
2	72 (7.1)	35 (7.1)	37 (7.2)	
3	492 (48.8)	252 (51.1)	240 (46.5)	
4	392 (38.9)	185 (37.5)	207 (40.1)	
5 (the least serious health condition)	34 (3.4)	12 (2.4)	22 (4.3)	
Peripheral oxygen saturation at entrance, mean (SD)	98.3 (3.2)	97.9 (3.7)	98.7 (2.4)	<0.001
Temperature at entrance (°C), mean (SD)	38.1 (15.2)	37.7 (1.0)	38.4 (21.3)	0.41
Hospitalization, n (%)	764 (75.7)	279 (56.6)	485 (94.0)	<0.001
Days since symptom onset, mean (SD)	2.3 (3.1)	2.9 (3.5)	1.52 (2.2)	<0.001
Contact with confirmed case, n (%)	72 (7.1)	58 (11.8)	14 (2.7)	<0.001
Positive cases, n (% of cases)	25 (34.7)	22 (37.9)	3 (21.4)	
Days since exposure, mean (SD)	6.0 (4.1)	6.0 (4.1)	5.9 (4.4)	0.92
Symptoms, n (%)				
Fever	502 (49.8)	343 (69.7)	159 (30.8)	<0.001
Nasal discharge	382 (37.9)	320 (65.2)	62 (12)	<0.001
Cough	355 (35.5)	314 (64.0)	41 (7.9)	<0.001
Diarrhoea	153 (15.2)	60 (12.2)	93 (18.0)	0.01
Comorbidities, n (%)				
Chronic respiratory disease	72 (7.2)	55 (11.2)	17 (3.3)	<0.001
Cardiopathy	30 (3.0)	19 (3.9)	11 (2.1)	0.15
Immunodepression	24 (2.4)	7 (1.4)	17 (3.3)	0.08

Symptomatic means the presence of a clinical picture compatible with severe acute respiratory syndrome coronavirus 2 infection, as described in the text. SD, standard deviation.

at bedside in the emergency service, as recommended by the manufacturer. Thereafter, the remaining of the NPA sample was sent to the hospital laboratory for RT-qPCR analysis (r-gene, bioMérieux) on an ABI7500 fast thermocycler (Thermofisher) after extraction of total nucleic acids using the NUCLISENS eMAG platform (bioMérieux).

During the outbreak of the respiratory syncytial virus (RSV), which started on 19 March, 2021 [20] and was still ongoing in August 2021, an AgPOCT (Veritor) was used 24/7 at the paediatric emergency department in children exhibiting a clinical picture of bronchiolitis, as previously described [19]. No influenza virus circulated during the study period; thus, the AgPOCT for an influenza diagnosis was not used.

According to the judgment of the physician in charge at the time of inclusion, some patients were also tested with the same NPA with a Luminex-based multiplex PCR assay (NxTAG Respiratory Pathogen Panel, Theradiag), which can detect 18 viruses (influenza virus A, influenza virus A H1N1pdm09, influenza virus A H3N2, influenza virus B, RSV-A, RSV-B, human parainfluenza virus (HPIV-1, HPIV-2, HPIV-3, HPIV-4), human coronavirus (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1), metapneumovirus, rhinovirus-enterovirus, adenovirus, and bocavirus) and three atypical bacteria (*Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*).

The AgPOCT results, combined with those of the RT-qPCR assay, including the Ct value for each gene target, were subsequently recorded. The Ct values were categorized according to the recommendations of the French Society of Microbiology for the r-gene assay as strongly positive (Ct < 23), positive ($23 \leq$ Ct < 33), or low positive (Ct $\geq$ 33) [21]. The study was approved by the local ethics committee (number IRBN332021/CHUSTE).

Statistical analysis

Continuous variables were expressed by their mean (standard deviation (SD)) and median (interquartile range) upon variable distribution. Categorical variables were presented by their frequencies and relative proportions. For comparisons of continuous variables, a parametric Student t test and nonparametric Mann–Whitney test upon variable distribution were used. For categorical variables, either a χ^2 or Fisher exact test was performed, depending on applicability. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated with 95% confidence interval (CI). The overall concordance was determined by the unadjusted Cohen's κ test and the prevalence- and bias-adjusted κ test. Statistical significance was defined as $p < 0.05$.

To obtain a sensitivity of 70% with a power of 0.810, the number of patients who tested positive was estimated at 49. With a disease prevalence of 5%, the total number of patients needed was 990. All statistical analyses were performed with R V4.0.2 software (GNU General Public License, https://www.r-project.org).

Results

Characteristics of the study population

The main demographic, anamnestic, clinical, and microbiologic characteristics of the 1011 included children are depicted in Table 1. The median age was 1.7 years (IQR, 0.4–5.2 years). The first reason for testing was the presence of symptoms compatible with COVID-19, with almost half of the study population presenting with fever. Data were missing for two patients; thus, 493 (48.9%) and 516 (51.1%) children were classified in the symptomatic and asymptomatic groups, respectively (Table 1).

After exclusion of 21 missing data points (two NPA failures and 19 omitted SARS-CoV-2 RT-qPCR prescriptions), the virological results were analyzed for a total of 990 children. SARS-CoV-2-postive results were obtained for 33 children (3.3%) with AgPOCT and for 46 children (4.6%) with RT-qPCR, with mostly low Ct values (Table 2; Fig. 1). During the study period, the incidence of new cases as defined by the French Health authorities was 105 to 215 cases per 100 000 inhabitants in the paediatric population of the Loire department (data available at data.gouv.fr). At this time, the alpha variant of SARS-CoV-2 predominated.

Performance of AgPOCT compared with RT-qPCR in the overall population

AgPOCT's sensitivity was 69.6% (95% CI, 54.3–82.3), and its specificity was 99.9% (95% CI, 99.4–100), with a negative predictive value of 98.5% (95% CI, 97.6–99.2) and positive predictive value of 97.0% (95% CI, 84.2–99.9; Table 3). The percent agreement was 98.5% (95% CI, 97.5–99.2). Given an overall concordance of 32 true positive cases and 943 true negative cases, the unadjusted Cohen's κ was 0.80 (95% CI, 0.74–0.86), and the prevalence-adjusted and bias-adjusted Cohen's κ was 0.97 (95% CI, 0.95–0.98).

Sensitivity varied according to the Ct value of the RT-qPCR assay (Fig. 1A). It was 100% (95% CI, 86.8–100) in strongly positive specimens and then decreased when the Ct value increased (Table 2; Fig. 2). Specificity was close to 100% (Fig. 2B), with a single AgPOCT false-positive result in a symptomatic 3-month-old child infected with RSV-A. Of note, the sample was not positive after retesting with AgPOCT.

SARS-CoV-2-infected symptomatic children

Among the 493 symptomatic participants (48.9%), the mean duration of symptoms at the time of testing was 2.89 days (Table 1). The most frequently registered symptoms were fever ($n = 343$; 69.7%), rhinorrhoea ($n = 320$; 65.2%), and cough ($n = 314$; 64.0%). Of note, no child presented with a severe form of COVID-19 infection. Thirty-five symptomatic patients (7.3%) were positive for SARS-CoV-2 infection on RT-qPCR (Table 2). The analysis disclosed a sensitivity of 82.9% (95% CI, 66.4–93.4) and a specificity of 99.8% (95% CI, 98.7–100) in this group (Table 3). As shown in Fig. 1B, the sensitivity of the AgPOCT was closely related to the Ct value of the RT-qPCR assay.

SARS-CoV-2-infected asymptomatic children

Among the 516 asymptomatic participants (51.1%) at the time of sampling, three (0.6%) tested positive on AgPOCT and 11 (2.1%) on RT-qPCR (Fig. 1B), with significantly higher Ct values than in symptomatic participants (Table 2). With a sensitivity of only 27.3% and a specificity of 100%, false-negative AgPOCT mainly happened in the asymptomatic group (Table 3).

Discussion

In comparison with RT-qPCR, the overall sensitivity and specificity of the AgPOCT were 69.6% (95% CI, 54.3–82.3) and 99.9% (95% CI, 99.4–100), respectively. With regard to children exhibiting symptoms compatible with COVID-19, the sensitivity increased to 82.9% (95% CI, 66.4–93.4), which is better than that recorded in previous studies where sensitivity ranged from 45% to 78% [15–17]. This high sensitivity meets the criteria recommended by the WHO for the use of an antigen test as a SARS-CoV-2 diagnostic technique [22]. In contrast, the sensitivity of the AgPOCT was very poor in asymptomatic patients.

Table 2
Virological results of SARS-CoV-2 infection in the children included in the study

	Overall (N = 1009)	Symptomatic (n = 493)	Asymptomatic (n = 516)	p-value
Positive RT-qPCR, n (%)	46 (4.6)	35 (7.3)	11 (2.1)	<0.001
Ct value of nucleocapsid target, mean (SD)	24.0 (7.3)	22.2 (5.8)	29.8 (8.5)	0.002
Ct value of polymerase target, mean (SD)	24.2 (6.6)	22.7 (5.5)	29.2 (8.0)	0.005
Ct-value category, n (%)				0.034
Strong positive (Ct < 23)	26 (56.5)	23 (65.7)	3 (27.3)	
Positive (23 ≤ Ct < 33)	13 (28.3)	9 (25.7)	4 (36.4)	
Low positive (Ct ≥ 33)	7 (15.2)	3 (8.6)	4 (36.4)	
Positive AgPOCT, n (%)	33 (3.3)	30 (6.1)	3 (0.6)	<0.001
Ct value of nucleocapsid target, mean (SD)	19.9 (3.6)	20.1 (3.7)	17.9 (4.3)	
Ct value of polymerase target, mean (SD)	20.6 (3.3)	20.7 (3.3)	18.9 (1.7)	
Negative AgPOCT, n (%)	14 (1.4)	6 (42.9)	8 (57.1)	
Ct value of nucleocapsid target, mean (SD)	33.3 (4.1)	32.1 (4.6)	34.2 (4.6)	
Ct value of polymerase target, mean (SD)	33.0 (3.6)	32.3 (3.2)	33.6 (1.2)	
Concordance between RT-qPCR and AgPOCT, n (%)				<0.001
False negative	14 (1.4)	6 (1.3)	8 (1.6)	
False positive	1 (0.1)	1 (0.2)	0 (0)	
True negative	943 (95.3)	440 (92.4)	501 (97.9)	
True positive	32 (3.2)	29 (6.1)	3 (0.6)	

Symptomatic means the presence of a clinical picture compatible with SARS-CoV-2 infection, as described in the text. AgPOCT, antigen point-of-care test; Ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.
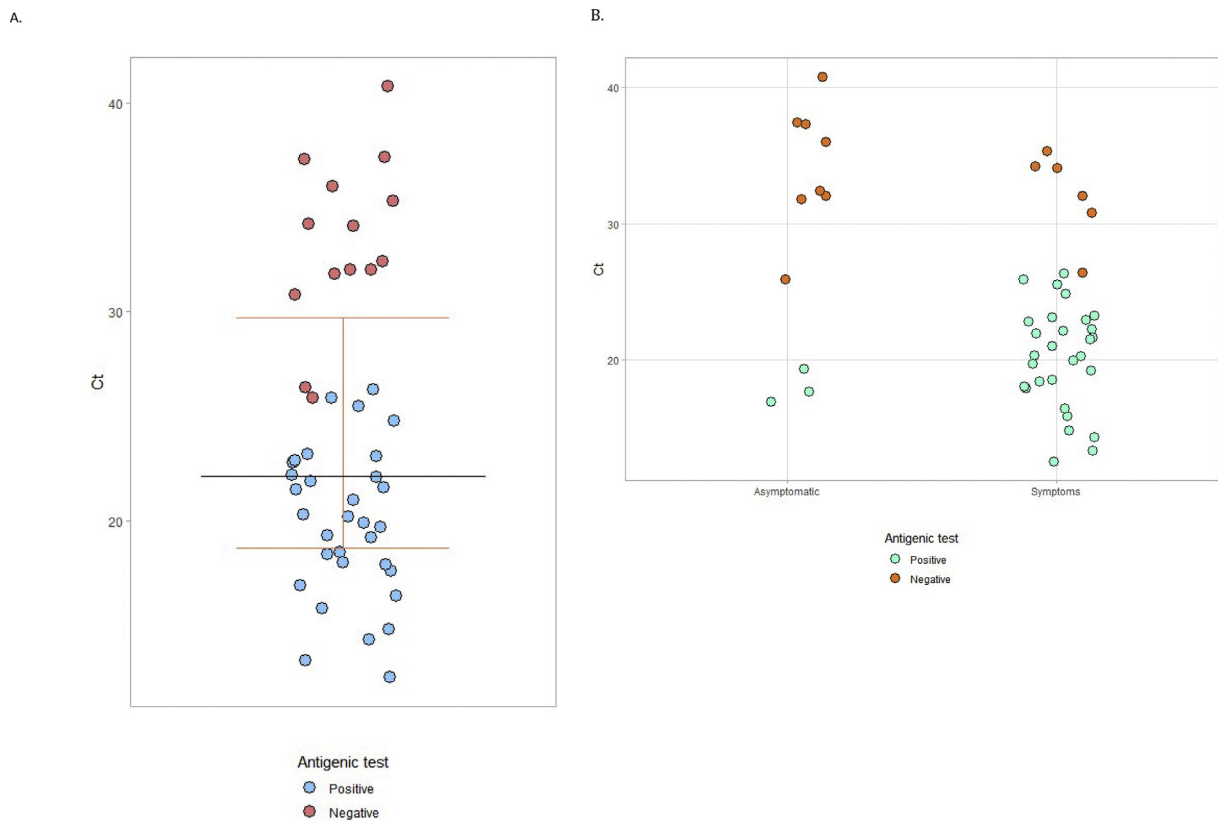
Fig. 1. Distribution of SARS-CoV-2 RT-qPCR Ct values after AgPOCT testing, globally (A) and according to the presence of symptoms (B). AgPOCT, antigen point-of-care test; Ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

As previously shown in adults and in children, Ct values were much lower in patients with a positive AgPOCT (true positives) than in those with a negative one (false negatives; Fig. 1). The correlation between low Ct values and high infectivity has been reported often previously [23–27], as also exemplified by the link between Ct value and *in vitro* culturability of the viral strain [28,29]. These considerations explain why the claimed sensitivity of a SARS-CoV-2 antigen test greatly depends on the Ct values of

the tested samples when RT-qPCR is used as a reference standard [8]. In addition, it is now well known that after the resolution of COVID-19 symptoms, people can have prolonged positive SARS-CoV-2 RT-qPCR results for several weeks, and Ct values are often very high at the end of the course of the disease [30]. Although these data have been mostly documented in adults, a similar long-lasting duration of low viral load (and thus high Ct value) may occur in children.

Table 3
Diagnostic accuracy of the COVID-19 speed antigen test in comparison with RT-qPCR

	Sensitivity (%), mean (95% CI)	Specificity (%), mean (95% CI)	Negative predictive value (%), mean (95% CI)	Positive predictive value (%), mean (95% CI)
Overall population	69.57 (54.25–82.26)	99.89 (99.41–100)	98.54 (97.56–99.20)	96.97 (84.24–99.92)
Strongly positive (Ct < 23)	100 (86.77–100)	—	—	100 (86.77–100)
Positive (23 ≤ Ct < 33)	46.15 (19.22–74.87)	—	—	100 (54.07–100)
Low positive (Ct ≥ 33]	0 (0–40.96]	—	—	0 (0–40.96)
Symptomatic	82.86 (66.35–93.44)	99.77 (98.74–99.99)	98.65 (97.09–99.50)	96.67 (82.78–99.92)
Asymptomatic	27.27 (6.02–60.97)	100 (99.27–100)	98.43 (96.93–99.32)	100 (29.24–100)

Symptomatic means the presence of a clinical picture compatible with severe acute respiratory syndrome coronavirus 2 infection, as described in the text. CI, confidence interval; Ct, cycle threshold.
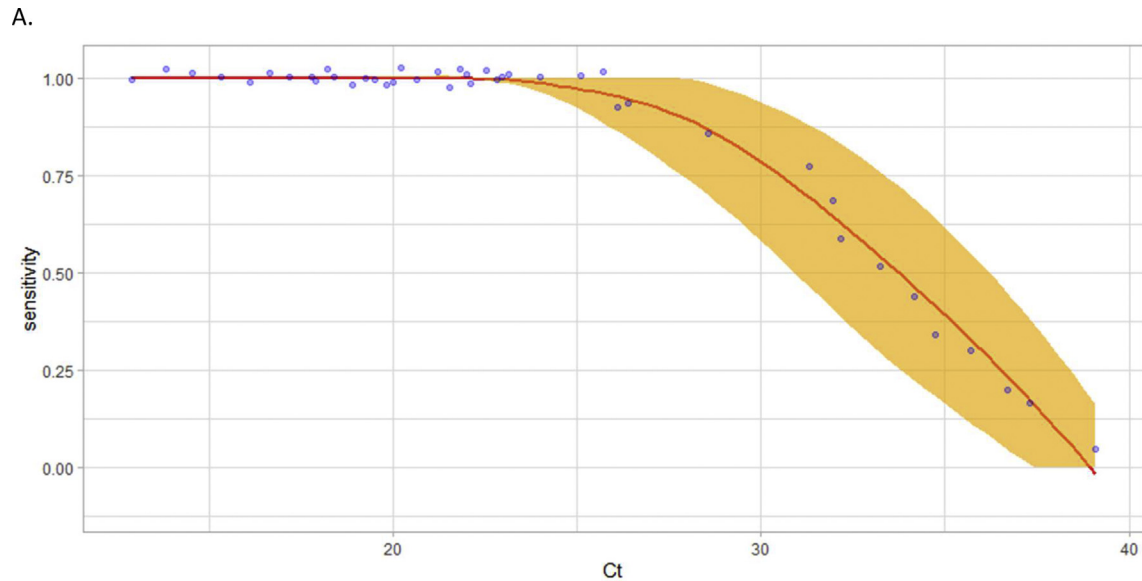
Fig. 2. AgPOCT sensitivity according to RT-qPCR Ct value. AgPOCT, antigen point-of-care test; Ct, cycle threshold.

Considering Ct value in association with the clinical context of patients might be helpful in individual management decisions, even if a negative result cannot exclude children at the very onset of their disease. The better sensitivity of the AgPOCT used in this study compared with previous data using tests based on the same technology could be due in part to the good performance of this particular assay, but also to the fact that the alpha variant of SARS-CoV-2 circulated preferentially during the study period, and this variant has been shown to exhibit higher viral loads [31].

Our study has also some limitations. The number of positive samples was limited by the low prevalence of SARS-CoV-2 infection during the study period, which reduces the statistical power of the analysis. Second, we analyzed a single commercial rapid test; despite the satisfactory performance of the COVID-19 speed antigen test, our conclusions cannot be extended to other commercial brands, implying that the performance of an antigenic test must be assessed very carefully before being used as a point-of-case test at bedside. Third, our study is monocentric by construction, which increases the risk of methodological weaknesses. Finally, the WHO international standard was not used to convert the Ct values of the PCR assay in international units per millilitre [27].

In conclusion, our results assess the acceptable sensitivity and specificity of the COVID-19 speed antigen test in symptomatic children. Consequently, the AgPOCT could be used in efforts to limit the viral spread in paediatric emergency settings. At our institution, the AgPOCT is presently used in all children exhibiting symptoms compatible with COVID-19 at the emergency department. Although additional studies are necessary to confirm our results, this study supports incorporating AgPOCT testing at the bedside in the emergency room into paediatric clinical guidelines to mitigate the SARS-CoV-2 pandemic.

Author contributions

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.12.019.

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