




Agreement between diagnostic methods for SARS-CoV-2 infection in children seen at the Emergency Department of a children's hospital

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ABSTRACT

Introduction. Rapid antigen tests (RAGTs) for SARS-CoV-2 are considered adequate for diagnosis at the point of care. Our objective was to establish the agreement between reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and RAGTs in the pediatric population.

Population and methods. All patients aged 1 month to 17 years and 11 months seen at the Emergency Fever Unit of a children's hospital between 6-11-2021 and 10-3-2021 were recruited. The Panbio COVID-19 Ag[®] test (Abbott Diagnostic) was compared to the reference method RT-qPCR (as per the protocol suggested by the United States Centers for Disease Control and Prevention).

Results. A total of 6491 patients were included. The prevalence of COVID-19 was 2.8%. Symptoms were observed in 92.1%. Sensitivity, specificity, and the kappa index of agreement for the RAGT were 71.0%, 99.9%, and 0.813, respectively. The kappa index and the RAGT sensitivity were significantly higher in the group aged 13–17 years (0.89 and 82.4%, respectively) compared to the groups aged 0–5 and 6–12 years. This may be due to the lower viral load observed in patients younger than 12 years.

Conclusion. Although RAGTs shorten the time to result and improve the isolation strategy for COVID-19 patients, their sensitivity in children younger than 12 years or asymptomatic children is not within the recommended ranges, especially during periods of low disease prevalence.

Key words: COVID-19 test, COVID-19, SARS-CoV-2, diagnostic reagent kit.

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INTRODUCTION

Rapid detection, effective isolation of symptomatic cases, and systematic close contact tracing are paramount to prevent the community dissemination of severe acute respiratory coronavirus 2 (SARS-CoV-2). Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) is the gold standard method for SARS-CoV-2 diagnosis.² However, it requires complex equipment, trained technicians, and a minimum time to obtain the result of 6 hours. In this context, rapid antigen tests (RAGTs) are more suitable for point-of-care diagnosis, as they allow obtaining the result within 15 minutes. These tests detect virus proteins, such as viral nucleocapsid or S-protein in respiratory samples obtained by nasopharyngeal or nasal swabbing. Available data on the sensitivity and specificity of RAGTs for SARS-CoV-2 were obtained from studies of varying designs that assessed tests of different brands. This results in reported sensitivities ranging from values below 20% (mostly in asymptomatic patients) to above 97% in symptomatic subjects and high-prevalence settings.^{3–14} According to the available evidence, RAGTs would be most useful in patients with a high viral load.^{3,15–20} Based on these observations, the World Health Organization (WHO) recommends using RAGTs that demonstrate a sensitivity $\geq 80\%$ and a specificity $> 97\%$.²¹

It is essential to keep in mind that the analytical sensitivity and specificity of a diagnostic kit as

reported by the manufacturer do not always reflect its actual performance in a given population, so it is necessary to validate the test locally.²²

The RAgT has been used since April 2021 in symptomatic patients older than 12 years suspected of SARS-CoV-2 infection at the Emergency Fever Unit of Hospital de Niños Ricardo Gutiérrez. During the first 60 days since its implementation, the RAgT and RT-qPCR were used simultaneously. In this prior evaluation in 414 patients aged 12 to 17 years, the RAgT showed a 78.4% sensitivity (95% confidence interval [CI]: 69.6–85.6), a 97.4% specificity (95% CI: 94.9–98.9), a positive predictive value (PPV) of 91.6% (95% CI: 84.5–95.6), a negative predictive value (NPV) of 92.5% (95% CI: 89.6–94.6), and a kappa index of 0.79 (95% CI: 0.73–0.86) (data not published). Based on these results, measured in a setting with a high prevalence of COVID-19 (20.1%) and RAgT having demonstrated a sensitivity close to the value recommended by the WHO, it was proposed to use the RAgT to guide patient care and expedite patient isolation and/or hospitalization.

To date, there are few publications comparing the performance of RAgTs with the reference method (RT-qPCR) in the pediatric population; therefore, the primary objective of this study was to assess the agreement between the results of the Panbio COVID-19 Ag[®] test (Abbott Diagnostic) and those obtained by RT-qPCR in children aged 1 month to 17 years and 11 months. The secondary objective was to assess the RAgT performance by age range, according to the presence and duration of symptoms, and cycle threshold (Ct) values obtained in the RT-qPCR test.

POPULATION AND METHODS

This was a prospective, observational, diagnostic and analytical test performance assessment study. All patients who met the inclusion criteria seen at the Emergency Fever Unit of Hospital de Niños Ricardo Gutiérrez between 6-11-2021 and 10-3-2021 were enrolled consecutively; their assent/consent for participation was obtained.

The following variables were recorded: age, sex, reason for testing, presence and type of symptoms, time elapsed since symptom onset, presence of comorbidities, and RAgT and RT-qPCR results (Ct and viral load).

Inclusion criteria

Patients aged 1 month to 17 years and 11 months seen at the Emergency Fever Unit due to suspected SARS-CoV-2 infection, with or without symptoms and who had given their assent/consent for study participation.

Exclusion criteria

Acutely ill patients who required urgent treatment and patients with immunosuppression or acute-on-chronic comorbidities were excluded.

In symptomatic patients, samples were collected in the first 7 days after disease onset. Asymptomatic patients were included because they were detected during pre-surgical controls or were close contacts or were teenage parents acting as companions in closed areas or travels.

Nasopharyngeal swabs were collected in all patients; one for the RAgT, placed in the lysis buffer provided by the manufacturer, and other for the RT-qPCR, placed in saline solution. RAgT samples were analyzed in the laboratory installed at the Emergency Fever Unit and RT-qPCR were studied by the Virology section of the Central Laboratory.

The Panbio COVID-19 Ag[®] test (Abbott Diagnostic GmbH, Jena, Germany), is a lateral flow immunochromatographic assay targeted at the SARS-CoV-2 nucleoprotein. Molecular detection by RT-qPCR developed based on the protocol proposed by the United States Centers for Disease Control and Prevention (CDC), which detects amplification of the RNA-dependent RNA polymerase (RdRp) gene/RNA helicase gene, and viral nucleoprotein gene; human ribonuclease P was used as an internal control. Results were expressed as Ct (point at which the fluorescence of the reaction exceeds the basal fluorescence) and as viral load. A Ct of less than 35 for the 3 genes was considered a positive test.

The technicians who performed the RT-qPCR were blinded to the RAgT result.

Ethical considerations

The study was approved by the hospital's Research Ethics Committee on June 10th, 2021. The parents or legal representatives of children younger than 6 years were asked to provide an informed consent. Children aged 6 to 12 years were also asked for their assent. Children aged 13 to 15 years were asked for their consent and their parents' or legal representatives' mandatory assent; and adolescents aged 16 and 17 years were asked to sign the consent together with their parents or legal representatives.²³

Methodological aspects

Results were reported in accordance with the STARD 2015 guidelines²⁴ and the recommendations by Hess et al.²⁵ The sample size was calculated using the MKmisc[®] package, which applies the formula suggested by Flahault et al.²⁶ A sensitivity of 80%, a power of 90%, an alpha of 5%, and a prevalence of 25% were the parameters included, which resulted in a sample size of $n = 700$.

Statistical analysis

The open-source R software, version 4.0.5[®]; the Rstudio interface, version 1.1.463[®]; and the Tidyverse, Qwraps2, and DescTools[®] packages were used. The sample was described using mean and standard deviation (SD) or median and interquartile range (IQR) for numerical variables, based on the observed distribution, and percentage and 95% confidence interval (CI) for nominal variables. The RAgT's sensitivity, specificity, PPV, and NPV were assessed. Cohen's kappa index was estimated to assess the agreement between methods.²⁷ A kappa index between 0.61 and 0.80 was defined as adequate agreement and between 0.81 and 1.00, as very adequate. Numerical variables were compared between groups using Student's t test or the Wilcoxon rank-sum test; nominal variables were compared between 2 groups using the χ^2 test or Fisher's test, as applicable. A value of $p < 0.05$ was considered statistically significant.

RESULTS

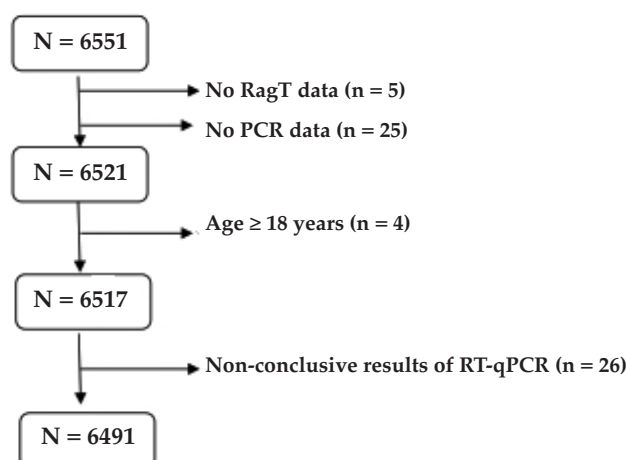
Although the sample size had been calculated at 700 patients considering a 25% estimated prevalence of COVID-19 positive cases, given the decrease in prevalence during the study period, the sample size had to be increased to reach a significant number of positive cases. Initially, 6551 patients were included; of these, 34 were excluded due to incomplete data or because they were outside the study age range and 26 due to inconclusive RT-qPCR results (Figure 1). The main reasons for consultation were meeting the definition of close contact or suspected COVID-19 case (92.7%), pre-surgical patients (6.3%), patients with acute respiratory disease (2.9%), and children in homeless shelters (0.6%).

Their median age was 4 years (IQR: 2–8 years), 52.6% were males. Table 1 shows the clinical and demographic characteristics of patients by age range. In total, 92.1% of subjects were symptomatic. The most common symptoms in the entire population, regardless of age, were cough (63.6%), rhinitis (56.4%), fever (47.6%), and odynophagia (31.5%) (Figure 2).

The prevalence of COVID-19 in the total sample based on the RT-qPCR was 2.8% (95% CI: 2.4–3.3). A marked reduction in prevalence was observed during the study period, decreasing from 18.4% in epidemiological week 24 to 0.3% in epidemiological week 35.

Table 2 shows the values of sensitivity, specificity, PPV, NPV for the RAgT, the Kappa index of agreement, Ct, and viral load obtained

FIGURE 1. Flowchart of included participants



for the entire sample and by age subgroups. The agreement between methods was adequate in the 0 to 5 and 6 to 12 years groups (kappa index: 0.77 and 0.79, respectively) and very adequate in the 13 to 17 years group (kappa index: 0.89).

Based on the WHO recommendations regarding the desired performance for a RAgt, the test assessed here showed an excellent specificity (> 97%) in all groups and an acceptable sensitivity (> 80%) only in the group aged 13–17 years. The assessment of the Ct and viral load values in the different groups showed a significant decrease in the Ct and a significant increase in the viral load in the group aged 13–17 years compared to the values found in patients younger than 12 years (Table 2).

When the comparison was made considering the presence or absence of symptoms, regardless of the age range, it was observed that the kappa index and the sensitivity of the RAgt were significantly higher in symptomatic patients (Table 3). In these patients, the Ct was higher

compared to asymptomatic patients (23.29 ± 6.77 versus 30.29 ± 6.08 ; $p < 0.01$).

Regarding the performance of the RAgt considering the duration of symptoms at the time of the test, no difference was found between those cases in which there was agreement between methods (2.5 ± 4.0 days) and those in which there was no agreement (2.4 ± 2.0 days).

Among the 183 samples that tested positive by RT-qPCR, the group that presented discordance between methods (positive RT-qPCR and negative RAgt) showed a mean Ct significantly higher than the mean Ct of the group with both positive tests (29.17 ± 4.89 versus 20.39 ± 4.39 ; $p < 0.05$).

No adverse events or complications were observed during the study conduct.

DISCUSSION

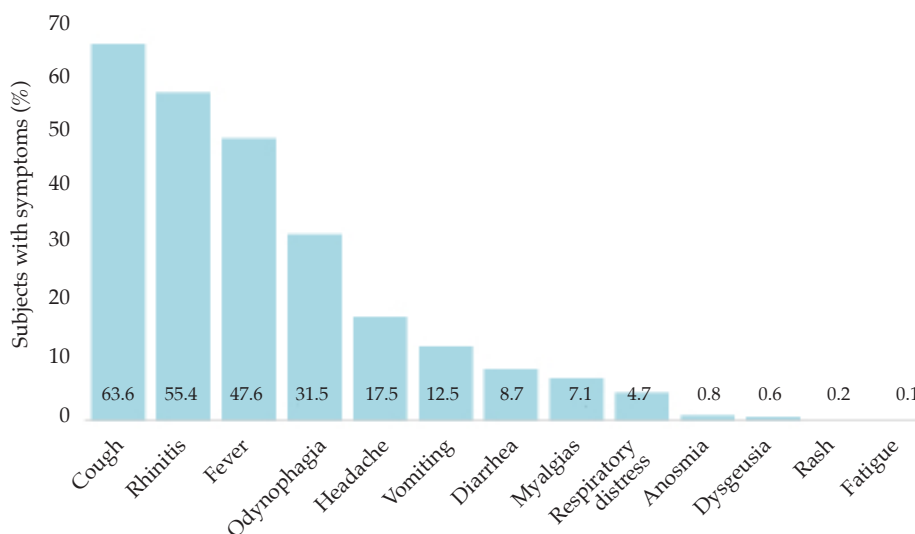
Since its onset, the COVID-19 pandemic has forced laboratories to increase the number of tests performed and shorten the time to result. Patients with compatible symptoms require rapid triage

TABLE 1. General characteristics of the study population by age group

Characteristics	0–5 years (n = 3969)	6–12 years (n = 1869)	13–17 years (n = 679)
Female sex, n (%)	1837 (46.3)	899 (48.1)	355 (52.3)
Comorbidities, n (%)	84 (2.1)	60 (3.2)	30 (4.4)
Clinical variables			
Symptomatic patients, n (%)	3769 (95.0)	1676 (89.7)	555 (81.7)
Days elapsed between symptom onset and medical consultation, median (IQR)	2 (2-3)	2 (1-3)	2 (1-3)

IQR: interquartile range.

FIGURE 2. Prevalence of symptoms in children and adolescents with coronavirus disease 2019 (n = 5978)



to expedite care and isolation, as well as contact tracing.

In September 2020, the National Drug, Food and Technology Administration of Argentina approved the use of the Panbio® COVID-19 Ag RAgT for the detection of SARS-CoV-2 in people suspected of COVID-19. These tests do not require complex equipment and provide results within 15 minutes. This makes them an important tool for mass-scale testing in different community settings.

A study conducted in Switzerland in 532 patients described the implementation of RAgTs in the Emergency Room of a teaching hospital.²⁸ Four RAgTs were used (Standard Q COVID-19 Rapid Antigen Test-SD Biosensor® [Roche Laboratories, Korea], Panbi® COVID-19 Ag Rapid Test® [Abbott Laboratories, USA], Exdia COVID19 Ag Precision Biosensor Inc.® [Daejeon Laboratories, Korea], and SARS-CoV-2 BD Veritor System® [Becton Dickinson Laboratory, USA]). The sensitivity obtained with the different diagnostic kits ranged between 48.3% and

41.2% for symptomatic patients, and was 33% for asymptomatic patients. All kits showed a specificity greater than 99%. When sensitivity was assessed in relation to viral load, it was observed it increased to more than 64% for viral loads higher than 105 copies/mL, to 95% for viral loads higher than 106 copies/mL, and reached 100% for viral loads higher than 107 copies/mL. The conclusion of that study is that, if a sensitivity greater than 80% is considered acceptable, none of the assessed RAgTs would reach that threshold in patients with a viral load below 106 copies/mL.

In a meta-analysis that assessed 133 studies that reported results from 112 323 samples analyzed, the overall sensitivity and specificity of the RAgTs used was 71.2% (95% CI: 68.2–74.0) and 98.9% (95% CI: 98.6–99.1), respectively.²⁹ Sensitivity increased markedly in samples with lower Ct values and was greater than 95% for Ct values below 25. Likewise, when patients were tested within the first week of symptom onset, sensitivity was higher (83.8%, 95% CI: 76.3–89.2) when compared to those tested after the first

TABLE 2. Performance parameters of the rapid antigen test and cycle threshold and viral load obtained in the reverse transcription-quantitative polymerase chain reaction tests for the overall sample and by age range

	All (n = 6491)	0–5 years (n = 3951)	6–12 years (n = 1862)	13–17 years (n = 678)
Kappa index (95% CI)	0.81 (0.77–0.86)	0.77 (0.68–0.86)	0.79 (0.71–0.87)	0.89 (0.82–0.96)
Sensitivity (%) (95% CI)	71.0 (63.89–77.49)	63.5 (50.40–75.27)	69.6 (57.31–80.08)	82.4 (69.13–91.60)
Specificity (%) (95% CI)	99.9 (99.82–99.97)	99.9 (99.86–99.99)	99.8 (99.51–99.97)	99.8 (99.11–99.99)
PPV (%) (95% CI)	96.3 (91.57–98.79)	97.6 (87.14–99.94)	94.1 (83.76–98.77)	97.7 (87.71–99.94)
NPV (%) (95% CI)	99.17 (98.91–99.37)	99.41 (99.12–99.63)	98.84 (98.23–99.28)	98.58 (97.33–99.35)
Ct (95% CI)	23.71 (21.92–25.50)	25.13 (23.17–27.09)	24.82 (22.98–26.66)	21.19 ^a (19.62–22.76)
Viral load (log ₁₀ /copies/mL) (95% CI)	7.758 (7.439–8.077)	7.676 (7.120–8.272)	7.329 (6.761–7.897)	8.244 ^b (7.756–8.732)

^ap < 0.01.

^bp < 0.05 for groups 0–5 years and 6–12 years.

CI: confidence interval, PPV: positive predictive value; NPV: negative predictive value, Ct: cycle threshold.

TABLE 3. Result of the comparison between rapid antigen test and reverse transcription-quantitative polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 by the presence or absence of symptoms at the time of sample collection

	Symptomatic (n = 5976)	Asymptomatic (n = 515)
Kappa index (95% CI)	0.8324 (0.79–0.88)	0.3290 (0.000–0.6711)
Sensitivity (%) (95% CI)	74.0 (66.78–80.35)	20.0 (2.5–55.6)
Specificity (%) (95% CI)	99.9 (99.8–99.9)	100.0 (99.3–100.0)
PPV (%) (95% CI)	96.2 (91.4–98.8)	100.0 (95.8–100.0)
NPV (%) (95% CI)	99.2 (98.9–99.4)	98.4 (96.9–99.3)

CI: confidence interval, PPV: positive predictive value; NPV: negative predictive value.

week (61.5%, 95% CI: 52.2–70.0).

It should be noted that studies that analyze agreement in the pediatric population are scarce. According to the Committee of Evidence-Based Pediatrics of the Spanish Society of Pediatrics on COVID-19, the performance of the RAgT should be considered a guiding test in patients with compatible symptoms for less than 5 days since onset, and RT-PCR should be performed if the result is negative and the diagnostic doubt persists.³⁰ The Committee also states that no recommendation can be established for its use in asymptomatic children since no evidence has been found for this indication.

The results obtained in this study performed in symptomatic and asymptomatic children younger than 18 years show a better performance of the RAgT in the group aged 13–17 years compared to the groups aged 0–5 and 6–12 years, possibly due to the lower viral load detected in these groups. A weakness of this study is the marked decrease in the prevalence of COVID-19 cases during the study conduct, which may have affected the performance of the RAgT.

The strategy for the use of the different diagnostic tests—either conventional or rapid—should be designed taking into account their availability, patient characteristics (symptomatic or asymptomatic, age, immunocompromise), the time since symptom onset, and the epidemiological moment during the pandemic. Thus, RAgTs may represent a useful resource in selected clinical settings, such as Emergency Departments, especially in periods of high prevalence of COVID-19, and be used as a complementary tool to RT-qPCR for a rapid patient classification.

CONCLUSIONS

Although RAgTs significantly shorten the time to obtain results and, therefore, the isolation period for SARS-CoV-2 patients, their sensitivity in children younger than 12 years or asymptomatic patients is not within the recommended ranges, especially during periods of low disease prevalence. ■

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