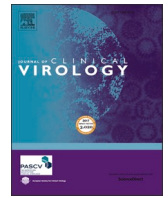




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## Evaluation of six commercial SARS-CoV-2 rapid antigen tests in nasopharyngeal swabs: Better knowledge for better patient management?

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### ABSTRACT

Robust antigen point-of-care SARS-CoV-2 tests have been proposed as an efficient tool to address the COVID-19 pandemic. This requirement was raised after acknowledging the constraints that are brought by molecular biology. However, worldwide markets have been flooded with cheap and potentially underperforming lateral flow assays. Herein we retrospectively compared the overall performance of five qualitative rapid antigen SARS-CoV-2 assays and one quantitative automated test on 239 clinical swabs. While the overall sensitivity and specificity are relatively similar for all tests, concordance with molecular based methods varies, ranging from 75,7% to 83,3% among evaluated tests. Sensitivity is greatly improved when considering patients with higher viral excretion ( $Ct \leq 33$ ), proving that antigen tests accurately distinguish infectious patients from viral shedding. These results should be taken into consideration by clinicians involved in patient triage and management, as well as by national authorities in public health strategies and for mass campaign approaches.

### 1. Introduction

Testing for SARS-CoV-2 infection is a critical tool to control COVID-19 spread, as it enables infected individuals to (self-)isolate and their contacts to quarantine [1]. The gold standard of COVID-19 diagnosis are molecular biology based techniques such as RT-PCR [2]. This method has several limitations, such as delayed results availability, the need for specialized laboratory equipment, as well as experienced technicians. As a result, appropriate management of positive cases can be delayed. Rapid antigen tests have been proposed as a complementary strategy to improve the capacities of SARS-CoV-2 infection diagnosis. However rapid antigen tests have lower sensitivity in comparison with RT-PCR and the potential benefit of their implementation can easily be jeopardized if they give false negative results [3–5]. Their clinical performances depend on different factors such as clinical setting use, local epidemiology and testing organizations. Several studies have shown a correlation between high cycle threshold (Ct) values or low viral load obtained by RT-PCR and a lower risk of contagiousness, mitigating the importance of solely working with highly sensitive tests. Rapid antigen tests are a diagnostic tool to perform widespread, repetitive and frequent testing that is crucial to harness COVID-19 [6]. Improved knowledge of

the analytical performance of rapid antigen tests is critical to better define their use strategy in a public health emergency setting. This retrospective study assessed the performance of six antigen tests compared to RT-PCR in a cohort of outpatients.

### 2. Materials and methods

#### 2.1. Study design

We conducted a retrospective study to determine the diagnostic performance of five rapid antigen tests and one automated quantitative antigen assay compared to RT-PCR. All nasopharyngeal swabs were collected by trained healthcare professionals from outpatients attending a specific SARS-CoV-2 diagnostic facility. Swabs were transferred into a Phosphate buffered saline (PBS) medium (Vacuette® Greiner bio-one) and were divided in 2 aliquots of 1.5 mL immediately after reception at the laboratory. One was used for the routine RT-PCR assay and the second made available for antigen tests evaluation and stored for a few hours refrigerated (+4 °C). According to the RT-PCR result, positive and negative swabs for SARS-CoV-2 RNA detection were selected to obtain a ratio close to 1 negative:1 positive, and then analysed by all the antigen

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tests. Delays between nasopharyngeal sample collection and rapid antigen tests never exceeded 12 h. Twenty-six positive swabs for respiratory pathogens other than SARS-CoV-2 (Supplementary table S1) were also retrospectively investigated to assess potential false positives. These samples have been stored at  $-80^{\circ}\text{C}$  for a maximum period of 12 months.

All patients were informed and did not oppose to participate in this protocol. Clinical data (age, sex, symptoms and onset of symptoms) were collected and stored according to local ethic procedures. Study protocol has been reviewed and approved by local ethic committee.

### 2.2. SARS-CoV-2 RNA detection

Two different methods were used to detect SARS-CoV-2 RNA genome in nasopharyngeal swabs according to routine lab organization. For one, nucleic acid was extracted from nasopharyngeal samples using the eMag automated system (BioMérieux, Marcy-l'Etoile, France). Amplification of SARS-CoV-2 RNA was performed using the RT-PCR assay developed by the French National Reference centre [7] on a LightCycler480 II platform (Roche Diagnostics, Mannheim, Germany). The second method was the Alinity m SARS-CoV-2 assay (Abbott Illinois, Chicago, USA).

The molecular diagnosis of respiratory viruses other than SARS-CoV-2 has been performed using multiplexed RT-PCR assays (BioFire™ FilmArray, BioMérieux; RespiFinder® 2Smart, PathoFinder; RealStar® Flu & VRS, Altona Diagnostics). Estimation of SARS-CoV-2 viral loads were obtained using the results of external quality controls acquired from Quality Controls for Molecular Diagnostics (QCMD, Glasgow, Scotland) [8]. Ct values were normalized against the French national reference RT-PCR. A Ct value of 32 corresponds to a viral load of  $2.99 \log_{10}$  RNA copies/mL ( $S.D \pm 0.0707$ ). Establishing a linear regression between Ct values (y-axis) and RNA viral load expressed in log copies/mL (x-axis), we found the following equation  $y = -2.66 x + 39.94$  ( $r^2 > 0.98$ ) (data not shown).

### 2.3. Antigen tests

Samples were analysed using five different rapid antigen tests and one automated quantitative antigen test, according to the manufacturers' recommendations. The characteristics of each test are shown in Table 1. Rapid antigen test results were assessed by trained staff after 10 to 30 min, according to manufacturer's instructions. Samples that yielded uninterpretable results were immediately retested in order to obtain either a positive or negative result. Only four Lumipulse assays failed due to an insufficient volume used as input in the automate.

Contrarily to others tests based on immunochromatographic methods, Lumipulse® G SARS-CoV-2 Ag kit (Fujirebio®, Japan) is a semi-quantitative and automated assay. For this assay, the positive threshold was initially set at 1.34 pg/mL, according to the manufacturer's recommendations.

**Table 1**  
Characteristics of the different antigenic assays.

| Name                                  | Manufacturer   | Distribution | Target | Technology               | Volume (μL) | Read Time (minutes) | Country of Manufacture |
|---------------------------------------|----------------|--------------|--------|--------------------------|-------------|---------------------|------------------------|
| Panbio™ COVID-19 Ag RAPID TEST DEVICE | Abbott®        |              | N      | Lateral flow immunoassay | 150         | 15                  | Germany                |
| SARS-CoV-2 Rapid Antigen Test         | SD Biosensor   | Roche®       | N      | Lateral flow immunoassay | 350         | 15                  | Republic of Korea      |
| SARS-CoV-2 one step card test         | Certest Biotec | Theradiag    | N      | Lateral flow immunoassay | 150         | 10                  | Spain                  |
| Coronavirus Ag rapid cassette         | Orient gene    | Menarini®    | N      | Lateral flow immunoassay | 150         | 15                  | China                  |
| Espline® SARS-CoV-2                   | Fujirebio®     |              | N      | Lateral flow immunoassay | 150         | 25–30               | Belgium                |
| Lumipulse® G SARS-CoV-2 Ag kit        | Fujirebio®     |              | N      | chemiluminescence CLEIA  | 250         | 35                  | Japan                  |

N: SARS-CoV-2 Nucleoprotein.

### 2.4. Statistical analysis

Sensitivity, specificity and concordance of rapid antigen tests were calculated using RT-PCR as reference method and following:

Sensitivity: True positive (TP)/ (TP+ False negative (FN))

Specificity: True Negative (TN)/ (TN+ False positive (FP))

Concordance: (TP+TN) / (TP+FN+TN+FP)

Based on the recommendations of the French society of microbiology and previous reports, the Ct of 33 was considered of interest to evaluate the contagiousness of SARS-CoV-2 infected patients [9-16]. modeling analyses were performed on GraphPad V5 (Prism, La Jolla, USA) using second order polynomial representation. The sensitivities of the different tests were compared using a Chi-square test or measuring the difference between two proportions (Z-test), when appropriate.

### 3. Results

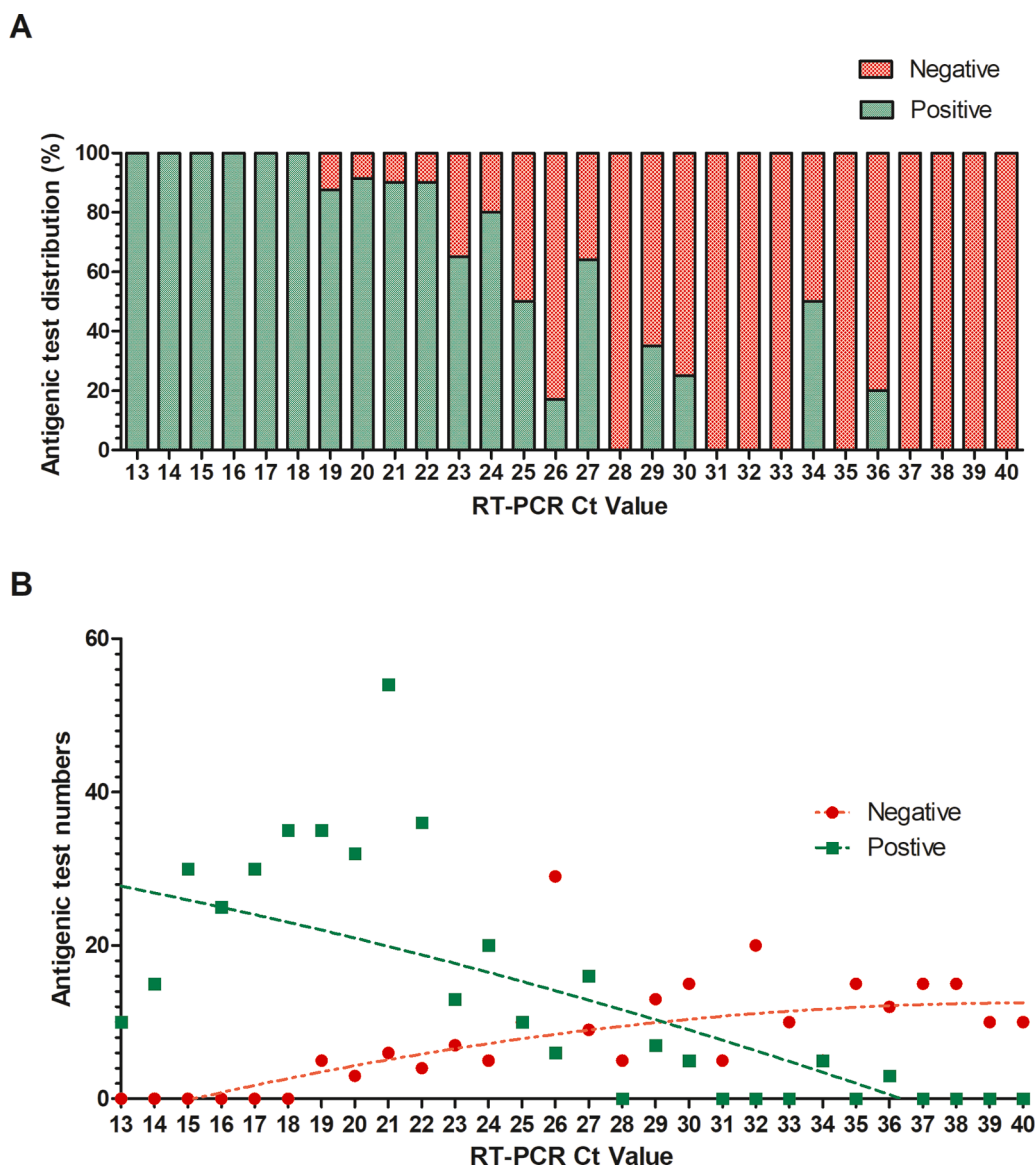
A total of 239 samples previously tested by RT-PCR were analysed with the 6 antigen tests. Among these patients, 40.2% (96 on 239) were healthcare professionals. The study population included 51.9% (124 out of 239) of patients with a positive result according to RT-PCR assay and a vast majority of symptomatic patients (64.4%) (Table 2). Among the 35 asymptomatic patients, 30 patients had a negative result for RT-PCR testing and five had positive results.

Among the results of 1195 qualitative rapid antigenic tests, 388 were positive (32.5%) and 807 were negative (67.5%). Among them, five hundred seventy negative tests with rapid antigen assays were also negative for RT-PCR. The distribution of antigen test results according to the Ct results of RT-PCR is shown at Fig. 1A and 1B. Only one assay yielded a false positive result (SD biosensor® one). The incriminated sample has been controlled a second time by RT-PCR and was confirmed to be a true negative. Interestingly, this sample was positive for human metapneumovirus. Taken together, the five qualitative antigen tests results showed a homogeneity in performance ( $p = 0.12$ ) (Table 3).

**Table 2**  
characteristics of the cohort.

| RT-PCR results                                       | Negative n (%) | Positive n (%) | Total n (%) |
|--|----------------|----------------|-------------|
| Asymptomatic patients                                | 30 (12.6)      | 5 (2.1)        | 35 (14.6)   |
| Symptomatic patients: 0 or 1 day after the onset     | 4 (1.7)        | 17 (7.1)       | 21 (8.8)    |
| Symptomatic patients: 2, 3 or 4 days after the onset | 31 (13.0)      | 73 (30.5)      | 104 (43.5)  |
| Symptomatic patients: 5 to 7 days after the onset    | 13 (5.4)       | 16 (6.7)       | 29 (12.1)   |
| Unknown status                                       | 37 (15.5)      | 13 (5.4)       | 50 (20.9)   |
| Total  | 115            | 124            | 239         |

% is expressed on the total population of the cohort ( $n = 239$ ).



**Fig. 1.** Results of antigen tests according to the Ct value obtained by RT-PCR. **A)** Frequency distribution. **B)** Cumulative distribution of results obtained for the five qualitative rapid antigenic tests ( $n = 625$ ). R-square values of the regression curves were 0.67 (red curve) and 0.61 (green curve). The median Ct is 24.1.

However, using a pair-wise comparison analysis, we observed a lower sensitivity for Certest (53.2%) in comparison with Orient gene (67.7%) and Espline (66.9%) tests ( $p < 0.03$  and  $p < 0.03$ ). When considering samples with  $Ct \leq 33$ , the sensitivities of the five qualitative assays were higher, ranging from 61.9% to 78.1%. The quantitative Lumipulse assay showed higher sensitivity than all other qualitative assays ( $p < 0.001$ ). Finally, the overall concordance with molecular biology results were at 81.3%, 75.7%, 79.5%, 80.8%, 82.8%, and 83.3% for the Lumipulse®, Certest®, Panbio™, SD biosensor, Espline® and the Orient gene tests respectively.

We analysed the sensitivity according to the presence of symptoms, and the delay between sample collection and the onset of symptoms. The sensitivities of each test were higher in symptomatic patients group ( $n = 154$ , median Ct values 21.5) when compared to the group combining asymptomatic patients and patients with unknown status ( $n = 85$ , median Ct values 29.5) ( $p < 0.01$ ) (Fig. 2A). Analysing all of the 1434 results, the sensitivities appeared higher for the specimens collected closely from the onset of symptoms. However, this result was only significant for the Certest ( $p < 0.05$ , when comparing groups D0/D1 versus D5/D6/D7) and this could be attributed to its lower sensitivity as

described above (Fig. 2B, Table 2). For the PanBio assay, this trend did not reach statistical significance.

Focusing on the quantitative Lumipulse assay, and considering the recommended threshold of 1.34 pg/mL, the overall sensitivity, the specificity, and the concordance were 87.6% [CI95%: 81.7–93.5], 72.7% [CI95%: 63.4–82.0], and 81.3%, respectively. When considering positive samples with  $Ct \leq 33$ , the sensitivity of Lumipulse increased to 98.0% [CI95%: 95.3–100], specificity to 72.7% [CI95%: 63.4–82.0], and concordance to 86.3%. Using a ROC curve analysis and a dot plot representation (Fig. 3A, B), we showed that a threshold of 6.55 pg/mL could improve the specificity of this assay yielding values at 95.5% [CI95%: 91.1–99.8] but the sensitivity decreased at 81% [CI95%: 74.0–88.0]. However, the concordance was higher at 87.1%. Considering samples with  $Ct \leq 33$  with this new threshold, the concordance with RT-PCR results also improved (94.2%). It is to be noted that the time-to-result for the Lumipulse assay is longer than for rapid antigen tests, but similar to those of POC RT-PCR tests ( $\approx 30$  min). The specificity and sensitivity were 99.0% and 69.4% respectively when choosing a threshold of 87.7 pg/mL.

**Table 3**  
Performance of the 6 evaluated antigen tests.

|              |                  | Se% (95%CI)        | Sp% (95%CI)        | Concordance |
|--------------|------------------|--------------------|--------------------|-------------|
| PanBio       | Global (n = 239) | 60.5 (51.9, 69.1)  | 100 (100, 100)     | 79.5%       |
|              | Ct≤33 (n = 105)  | 70.5 (61.8, 79.2)  | -                  | -           |
| SD Biosensor | Global (n = 239) | 63.7 (55.2, 72.2)  | 99.1 (97.4, 100)   | 80.8%       |
|              | Ct≤33 (n = 105)  | 73.3 (64.9, 81.8)  | -                  | -           |
| Certest      | Global (n = 239) | 53.2 (44.4, 62.0)  | 100 (100, 100)     | 75.7%       |
|              | Ct≤33 (n = 105)  | 61.9 (52.6, 71.2)  | -                  | -           |
| Orient Gene  | Global (n = 239) | 67.7 (59.5, 76.0)  | 100 (100, 100)     | 83.3%       |
|              | Ct≤33 (n = 105)  | 78.1 (70.2, 86.0)  | -                  | -           |
| Espline      | Global (n = 239) | 66.9 (58.7, 75.2)  | 100 (100, 100)     | 82.8%       |
|              | Ct≤33 (n = 105)  | 77.1 (69.1, 85.2)  | -                  | -           |
| Lumipulse    | Global (n = 235) | 87.6* (81.7, 93.5) | 72.7* (63.4, 82.0) | 81.3%*      |
|              | Ct≤33 (n = 105)  | 98.0* (95.3, 100)  | -                  | -           |
|              |                  |                    |                    |             |

Se: sensitivity, Sp: specificity.

\* for the Lumipulse® assay the values were obtained considering a cut-off value at 1.34 pg/mL according to the manufacturer's recommendations.

**4. Discussion**

Antigen tests are an easy and rapid tool to perform diagnosis of SARS-CoV-2 infection. In the present study, we evaluated six commercially available antigen tests and compared these to RT-PCR results obtained for nasopharyngeal specimens from 239 outpatients. Our main finding yielded sensitivities ranging from 53.2% to 67.7% for qualitative tests and up to 87.6% for quantitative test.

Our work deliberately included similar proportions of positive and negative nasopharyngeal samples tested by RT-PCR. We found values of sensitivity ranging from 53.2% to 87.6% comparable to previous studies including samples with the same heterogeneity of RNA viral loads [17-21].

As expected, when considering stronger viral excretions (samples with Ct ≤ 33 in the RT-PCR result), the sensitivity improved for all assays with values ranging from 70% to 98%. In a recent study, the FujireBio® LumiPulse assay showed a sensitivity of 92.0% and a concordance of 99.7%, slightly higher than the results obtained here.

However, the frequency of included positive cases was lower (4%) than ours and the results between 1 and 10 pg/mL were considered as inconclusive [22]. Concerns about false positive results of the Lumipulse assay have been reported [23], also we did not unveil such cases.

Recently, the Panbio™ test from Abbott® was used in more than 1300 patients in The Netherlands and showed [18] a very high specificity (100%), thus confirming the specificity obtained in our study. In another study, the comparison of the Espline® test with other antigen tests, molecular biology or viral culture isolation concluded to misdiagnosis in about half positive specimens [3]. Nevertheless, this study was carried out on only 80 clinical specimens of various origin. A recent study compared 7 commercial tests in 238 clinical samples (2 of them were also used herein, the Panbio® and the SD biosensor assays), and the authors described a high specificity and good sensitivity [5], in accordance with our findings.

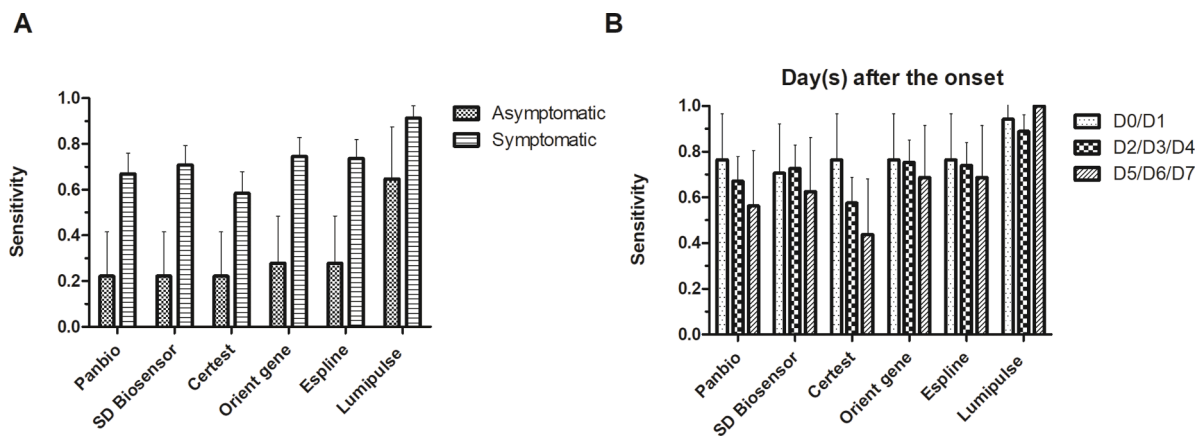
The question of how important the sensitivity of the assays is, is still debated [24,25]. The relatively poor sensitivity of antigen tests compared to RT-PCR can be overcome with a widespread and frequent testing strategy [26,27]. For highly contagious patients, i.e. those with high RNA viral load (higher than 3.8 log<sub>10</sub> copies/mL, Ct number below 25), the sensitivity of antigen tests exceeded 93% limiting the risk of misdiagnosis and mismanagement in the SARS-CoV-2 pandemic.

The Lumipulse assay delivered a quantification of antigen amount present in samples. This quantification showed a fairly good agreement with RT-PCR Ct numbers (R<sup>2</sup>=0.767, data not shown), thus offering a viable alternative to RT-PCR in settings where the latter is not available. However the cut off should be set higher to improve the specificity and the positive predictive value in a context of random massive screening tests where the prevalence of SARS-CoV-2 infection may be low. When setting a higher threshold to obtain a specificity of 99%, the sensitivity of this assay was comparable to others lateral flow assays.

In our evaluation, we observed only one false positive result with the SD biosensor assay. However, we could not determine the cause of this false positive test (cross reaction with human metapneumovirus versus other non-specific reaction). In our investigation, which included 17 samples with seasonal human coronaviruses, we did not find any misdetection, in particular with the closely-related betacoronavirus HKU1. This result was similar to the study of Corman et al. [5], besides they only tested two samples for human coronaviruses.

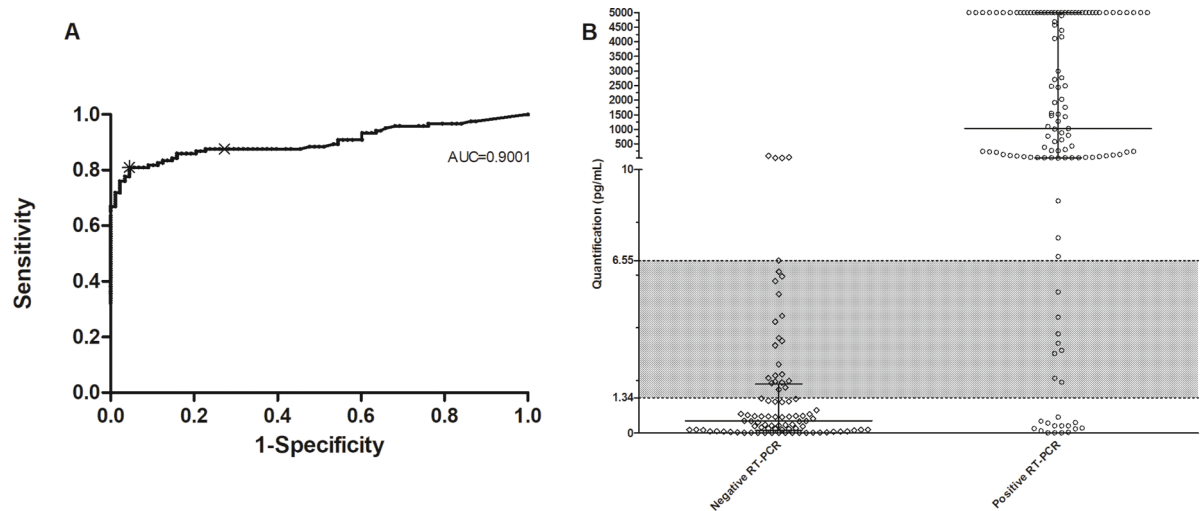
One of the advantages of qualitative antigen tests is their ease of use and we closely monitored the practical aspects of these assays. For Panbio™ test, we noted practical difficulties (leaks during liquid handling) raising a threat of cross contamination between tests, especially when performed in batches.

A limitation of our study stems from the retrospective selection of our population with an artificial overrepresentation of positive cases in RT-



**Fig. 2.** Sensitivity of the different antigenic tests according to presence of symptoms or the delay of testing after symptoms onset. In Fig. 2A, 85 swabs from asymptomatic patients or for which status was unknown were included for each assay. One hundred fifty-four symptomatic cases were included for all tests. For the Fig. 1B, details for each subgroup are indicated in table 2.





**Fig. 3.** Lumipulse® results obtained from 235 swabs. **A)** ROC curve **B)** quantitative values distribution according to the RT-PCR result. **A)** The asterisk point \* corresponds to a sensitivity of 0,805 and a specificity of 0,956 with a threshold of 6.55 pg/mL. The cross point indicates the recommended manufacturer's threshold of 1.34 pg/mL. **B)** Horizontal bars indicate the median value and error bars represent the interquartile range. One hundred fourteen samples were represented in the negative RT-PCR group and 121 in the positive RT-PCR group.

PCR. However, this approach enabled us to obtain a diversity of samples in term of viral RNA loads. As reported in other studies, the delay between the collection and the analysis of the swab stored refrigerated in PBS for a maximum of 12 h could affect the results of sensitivity [5,18,21].

In the future, with the need for point-of-care tests to quickly control epidemics due to emergent pathogens [28], clinicians should be aware of the performance of novel commercialized assays to guide them in their practices, and for the management of infected patients. Our result highlight that rapid antigen tests have a better sensitivity for the detection of symptomatic cases than asymptomatic cases. However, considering the kinetic of RNA viral load and the diagnosis window, tests should be repeated on different days.

Finally, mass rapid antigen test campaigns are one of the available epidemic control measures and they have shown incredible impact (i.e. Slovakia [27]), proving this strategy is efficient. Using better tests among those available will undoubtedly yield better outcomes for populations.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jcv.2021.104947](https://doi.org/10.1016/j.jcv.2021.104947).

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