



## Original Article

## Potential usage of anterior nasal sampling in clinical practice with three rapid antigen tests for SARS-CoV-2



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## ABSTRACT

**Introduction:** Anterior nasal sampling (AN) might be more convenient for patients than NP sampling to diagnose coronavirus disease. This study investigated the feasibility of rapid antigen tests for AN sampling, and the factors affecting the test accuracy.

**Methods:** This single-center prospective study evaluated one qualitative (ESP) and two quantitative (LUMI and LUMI-P) rapid antigen tests using AN and NP swabs. Symptomatic patients aged 20 years or older, who were considered eligible for reverse-transcription quantitative polymerase chain reaction using NP samples within 9 days of onset were recruited. Sensitivity, specificity, and positive and negative concordance rates between AN and NP samples were assessed for the rapid antigen tests. We investigated the characteristics that affected the concordance between AN and NP sampling results.

**Results:** A total of 128 cases were recruited, including 28 positive samples and 96 negative samples. The sensitivity and specificity of AN samples using ESP were 0.81 and 1.00, while those of NP samples were 0.94 and 1.00. The sensitivity of AN and NP samples was 0.91 and 0.97, respectively, and specificity was 1.00, for both LUMI and LUMI-P. The positive concordance rates of AN to NP sampling were 0.87, 0.94, and 0.85 for ESP, LUMI, and LUMI-P, respectively. No factor had a significant effect on the concordance between the sampling methods.

**Conclusions:** ESP, LUMI, and LUMI-P showed practical diagnostic accuracy for AN sampling compared to NP sampling. There was no significant factor affecting the concordance between AN and NP sampling for these rapid antigen tests.

## Authorship statement

Concept and design: H. Nomoto, K. Yamamoto Acquisition, analysis, or interpretation of data: H. Nomoto, K. Yamamoto Data collection: H. Nomoto, K. Yamamoto, Y. Miyazato, T. Suzuki, T. Maruki, G. Yamada, K. Kamegai, Y. Akiyama, S. Ide Drafting of the manuscript: H. Nomoto

Statistical analysis: H. Nomoto, K. Yamamoto Preparation and handling of specimens: E. Isaka, M. Kurokawa, A. Moriya, K. Mezaki, S. Yagi, H. Nojima, K. Yamakawa Supervision: N. Ohmagari Critical revision of the manuscript for important intellectual content: All authors. All the authors meet the ICMJE authorship criteria.

**Abbreviations:** COVID-19, coronavirus disease; AN, Anterior nasal sampling; NP, nasopharyngeal sampling; RT-qPCR, reverse-transcription quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ct, cycle threshold; IQR, interquartile range.

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## 1. Introduction

The standard reference test to diagnose coronavirus disease (COVID-19) involves the confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by reverse-transcription quantitative polymerase chain reaction (RT-qPCR) [1]. However, RT-qPCR testing is expensive and requires specialized equipment and adequate human resources. Rapid antigen testing for SARS-CoV-2 is superior to RT-qPCR in these aspects, and has a relatively high diagnostic accuracy in the early stage of the disease, which may contribute to disease management in the clinical and public health settings [2].

The standard sampling method for most rapid antigen tests is nasopharyngeal (NP) sampling, but this requires a trained medical professional for sample collection, and patients may experience discomfort during specimen collection. On the other hand, anterior nasal (AN) sampling might be less painful and more convenient for patients than NP sampling [3]. Some studies have examined the usefulness of AN sampling in health care facilities [4–6] and communities [7]. However, the feasibility of diagnosing COVID-19 using rapid antigen tests for AN samples and the factors affecting test accuracy require further investigation. The primary objective of this study was to evaluate the diagnostic accuracy of AN sampling compared to NP sampling using three different rapid antigen testing kits. Additionally, we evaluated the factors influencing the accuracy of rapid antigen tests using AN samples.

## 3. Methods

### 3.1. Study design and participants

This single-center prospective study evaluated the concordance of AN and NP swabs using one qualitative and two quantitative rapid antigen testing kits. The study was conducted at the National Center for Global Health and Medicine, a tertiary care hospital in Tokyo, Japan. The rapid antigen testing kits were approved by the Pharmaceutical Affairs Law as COVID-19-antigen test kits [8]. The qualitative rapid antigen test kit was Espline® SARS-CoV-2 (Fujirebio Inc, Japan) (ESP), which uses immunochromatography for detecting SARS-CoV-2 nucleoprotein. Lumipulse® SARS-CoV-2 Ag (LUMI) and Lumipulse® Presto® SARS-CoV-2 Ag (LUMI-P) (Fujirebio, Tokyo, Japan) were quantitative antigen tests based on the chemiluminescence enzyme immunoassay [9]. Symptomatic patients aged 20 years or older who were considered eligible for NP SARS-CoV-2 RT-qPCR testing within 9 days of onset were recruited in the study. Patients with a nasal cavity anatomy that was inappropriate for NP sampling were excluded. The following data of the patients were collected: age, sex, date of onset, history of antiviral medication at the time of collection, sampling method, and symptoms at the time of collection. In this study, the primary outcome variable can be considered a binary variable (accepted or rejected), and the total number of subjects required (N) is defined as [10]:

$$N = 4z_{\alpha}^2 P(1-P)/W^2$$

where P is the expected proportion with the characteristic of interest, W is the width of the confidence interval, and  $z_{\alpha}$  is a value from the normal distribution related to and representing the confidence level (equal to 1.96 for 95% confidence, in our case). In our study, we used  $W = 0.2$  and  $P = 0.95$  for sensitivity, and  $W = 0.04$  and  $P = 0.99$  for specificity. That way, considering the exclusion and declination, the numbers were set at 30 for the positive cases and 100 for the negative cases.

### 3.2. Sampling methods

The collection of NP and AN swabs was performed according to the guidelines for pathogen testing for COVID-19, published by the Ministry of Health, Labor, and Welfare [11]. Professional NP sampling was performed first, and then the participants could choose whether to undergo

self-sampling or professional sampling for the collection of AN swabs. We performed one AN sampling and one NP sampling per patient. For AN sampling, a swab was inserted about 2 cm along the nasal cavity, and the AN cavity was slowly wiped about 5 times. Then, the same swab was used to sample the opposite AN cavity in the same way. For self-sampling, clinicians supervised the patients during the procedure to ensure that they collected the AN samples properly. We collected NP and AN samples from both outpatients and inpatients. All samples were preserved as frozen samples and were analyzed later.

### 3.3. Procedures of RT-qPCR and rapid antigen testing

The reference standard to confirm COVID-19 was based on the result of RT-qPCR of a professionally-collected NP sample. A universal transport medium (1 mL; COPAN Diagnostics Inc., USA) was utilized as the viral transport medium.

The Cobas SARS-CoV-2 & Flu A/B assay on the 8800 platform (Roche Diagnostics, Indianapolis, IN) were used according to the instructions for use. Briefly, 600  $\mu$ L of specimen VTM was added to a barcoded secondary tube (12 by 75 mm) and loaded directly on the instrument. Using the calculated cycle threshold (Ct) value and PCR amplification efficiency of the NCOV-1 primer or SARBV-1 primer set, a correlation equation for the Ct value and the number of RNA copies were determined. The Ct value obtained from the reference material (SeraCare, AccuPlex™ SARS-CoV-2 Reference Material Kit) was used to perform a correction to calculate the number of RNA copies.

ESP, LUMI, and LUMI-P testing were performed according to the manufacturer's instructions (Fujirebio Inc.). Briefly, for ESP, we applied 20  $\mu$ L of pretreated samples onto the sample window of the reaction cassette, then pressed the convex button of the reaction cassette down immediately. After leaving the reaction cassette horizontally for 30 min, Fujirebio employees who had received training in Espline determination confirmed the pattern of lines on the interpretation window in a blinded manner without knowing the RT-qPCR results. At 30 min, when a blue reference line was observed and a blue test line appeared, it interpreted it as positive result, and when a blue reference line was observed but no blue line appeared, it was judged it as a negative result. For LUMI and LUMI-P, the collected specimens were centrifuged at 2000 $\times$ g for 10 min, and the supernatant was used for the test. We used 100  $\mu$ L of thawed samples to measure the antigen levels with a Lumipulse® G1200 for LUMI and Lumipulse L2400 for LUMI-P (Fujirebio Inc.). When the antigen level could not be measured as a result of exceeding the detection limit, we tested the diluted sample and then calculated the antigen level of the original sample. The lower detection limit was set at 1.34 pg/mL for LUMI and LUMI-P according to the currently recommended manufacturer's threshold value.

### 3.4. Statistical analyses

Discrete variables were expressed as numbers and percentages, while continuous variables were presented as medians and interquartile range (IQR). For each rapid antigen test, sensitivity, specificity, and the positive and negative concordance rates between AN and NP samples were calculated. The antigen levels between AN and NP sampling for LUMI and LUMI-P were compared using the Wilcoxon rank sum test. We also investigated the patient characteristics that can affect the concordance between AN and NP sampling results in rapid antigen tests. Fisher's exact test was performed to assess the concordance, with  $P < 0.05$  indicating a significant difference. Stata SE v17 (StataCorp LLC, Texas, USA) was used for all analyses, and IBM SPSS Statistics v26.0 (IBM Corp., Armonk, NY, USA) was used to create supplementary figures for the result of ESP with RT-qPCR and LUMI as the reference.

## 4. Ethics

This study was approved by the National Center for Global Health

and Medicine Ethics Review (NCGM-G-004058-01). We obtained written informed consent from all patients for participation in the study.

## 5. Results

A total of 128 patients were included, among whom 32 patients were positive and 96 patients were negative on SARS-CoV-2 PCR testing of NP samples (Table 1). We collected samples from January 21, 2021, to August 17, 2021. The median time from onset of symptoms to sampling was 2 days (IQR: 1–4 days). There were 125 mild cases (no oxygen demand), three moderate cases (oxygen demand but no ventilator requirement), and no severe case (ventilator required). For AN sampling for rapid antigen testing, 71 samples were professionally collected and 44 were self-sampled, while the methods used for collecting the remaining 13 samples could not be captured. Majority of the patients were not given antiviral medicines at sample collection, except for two patients, one of whom received remdesivir and the other dolutegravir/abacavir/lamivudine.

The results of rapid antigen testing for AN and NP samples are shown in Table 2. The sensitivity and the specificity of AN sampling using ESP were 0.81 and 1.00, respectively, while those of NP sampling were 0.94 and 1.00, respectively. The sensitivity of AN and NP samples was 0.91 and 0.97, respectively, which was the same for LUMI and LUMI-P. The specificity, on the other hand, was 0.97 for LUMI-P due to three samples being considered false positives. For ESP, the positive and negative concordance rates of AN to NP sampling were 0.87 and 1.00, respectively. Some cases that showed a discrepancy in the qualitative antigen test between NP and AN samples had low antigen or virus levels in the AN sample (Supplemental Figs. 1 and 2). AN samples tended to have lower viral and antigen levels, and the samples with discrepant results tended to have especially low viral levels, both in the AN and NP samples.

Antigen levels between AN and NP sampling were compared for the results of LUMI and LUMI-P (Fig. 1). For both rapid antigen kits, the antigen levels of NP sampling were significantly higher than those of AN sampling (median value: 3.75 for NP sampling and 2.21 for AN sampling in LUMI; 3.68 for NP sampling and 2.17 for AN sampling in LUMI-P) ( $P$ -value = 0.001 for both LUMI and LUMI-P).

Furthermore, we investigated the factors that affect the concordance between AN and NP sampling results in rapid antigen tests. The ESP results for AN and NP sampling are shown in Table 3. None of the analyzed factors was associated with a statistically significant difference in the concordance rate between the two sampling methods. The results of similar analyses for AN and NP sampling using LUMI and LUMI-P are

**Table 1**  
Demographics of COVID-19 and non-COVID-19 patients.

	COVID-19	Non-COVID-19	P-value
	N = 32	N = 96	
Age, years	50.5 (39.5–70)	31 (26.5–47)	<0.001
Sex, female	23 (72%)	44 (46%)	0.011
Days from onset to sample collection, days	5 (3–6)	2 (1–3)	<0.001
Symptoms at sample collection			
Fever	21 (66%)	35 (36%)	0.004
Any lower respiratory symptom	15 (47%)	16 (17%)	<0.001
Any upper respiratory symptom	11 (34%)	40 (42%)	0.47
Dysosmia or dysgeusia	9 (28%)	1 (1%)	<0.001
Sampling method <sup>a</sup>			<0.001
Self-sampling	20 (65%)	24 (29%)	
Professional sampling	11 (35%)	60 (71%)	

Categorical variables are expressed as numbers (percentage). Continuous variables are expressed as medians (interquartile range).

Abbreviations: COVID-19, coronavirus disease.

<sup>a</sup> Unknown for 13 samples.

shown in Supplementary Tables 1 and 2, respectively. No factor was found to affect the concordance between the two sampling methods for LUMI and LUMI-P.

## 6. Discussion

We studied the diagnostic accuracy of AN and NP sampling using three rapid antigen tests. AN sampling had a sensitivity and specificity equivalent to that of NP sampling for all rapid antigen tests, and a positive concordance rate of 0.87–0.94. The minimum performance criteria specified by the World Health Organization (WHO) for rapid antigen tests are a sensitivity of 80% and specificity of 97% [12]. The rapid antigen tests for AN sampling in our study basically met these criteria. Therefore, we believe that the performance of these rapid antigen tests using AN sampling is satisfactory for practical use.

The reported accuracy of rapid antigen tests using AN sampling has been variable to date. For qualitative antigen tests, two studies have been published on the diagnostic accuracy of AN sampling using the kit approved by the WHO for emergency use (STANDARD Q COVID-19 Ag Test, SD Biosensor, Inc., Korea). One study showed that the sensitivity and specificity of sampling from the nasal mid-turbinate were 80.5% and 98.6%, and the positive and negative concordance rates with NP sampling were 93.5% and 95.9%, respectively. On the other hand, another study reported that the sensitivity and specificity of professionally collected AN samples were 86.1% and 100%, respectively, and the positive and negative concordance rates to NP sampling were both 100% [13]. In a Japanese study using another rapid antigen kit (QuickNavi-COVID19 Ag, Denka Co., Ltd., Japan), the sensitivity of AN sampling was 72.5%, which was lower than the sensitivity of NP sampling (86.7%) reported in their former trial using NP samples [14,15]. However, AN sampling was shown to have the advantage of being less likely to induce coughs and sneezes. Espline SARS-CoV-2 Ag test based on immunochromatography was as accurate as reported in previous studies for AN sampling. It also has the same advantage of being less invasive, which may be beneficial for patients.

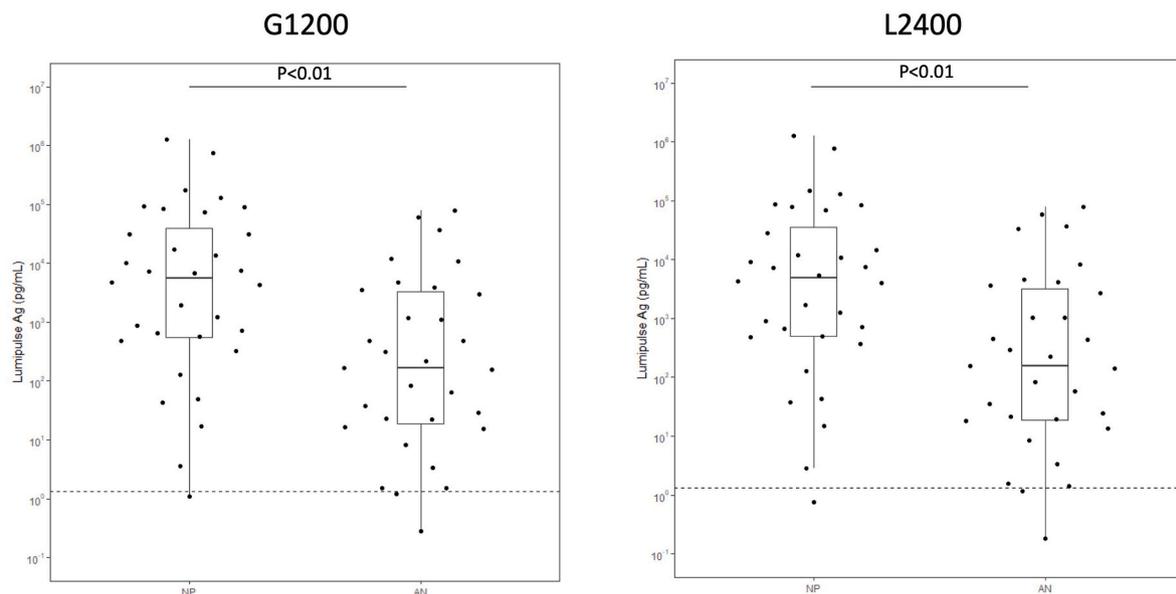
However, few studies have evaluated AN sampling using quantitative rapid antigen tests. Existing reports using NP samples have shown a diagnostic accuracy comparable to that found in the present study [16, 17]. Although AN sampling in the present study demonstrated significantly lower antigen levels than NP sampling, the diagnostic accuracy was comparable to that of NP sampling, at least within 9 days from the disease onset. The antigen test used in our study yielded 3/96 false positives with LUMI-P alone. The factors associated with false positives for LUMI and LUMI-P are not clear. However, a lower cutoff value could lead to false positives for such quantitative tests. Antigen values for these three samples were close to the cutoff. LUMI and LUMI-P can process several samples in a short time and have been used for quarantine testing at major airports in Japan and Germany [18]. The accuracy of AN sampling in our study was equal to or better than that of the salivary sampling, which has already been reported to be acceptable for practical use [19,20].

We analyzed the factors influencing the rate of concordance of rapid antigen tests between AN and NP sampling. There was no significant factor affecting the concordance between the two sampling methods for ESP, LUMI, and LUMI-P. However, ESP tended to show a lower concordance rate between AN and NP sampling among obese patients, who had a body mass index >25 kg/m<sup>2</sup>, suggesting the potential disadvantage of AN sampling in obese patients. It was not clear why obesity reduced the test accuracy of AN sampling. Obesity is associated with nasal blockage, which might negatively influence the result of AN sampling [21]. Nevertheless, AN sampling among patients with upper respiratory symptoms was likely to be consistent with NP sampling. There is a paucity of literature examining the association between specific symptoms and viral load in the nasal cavity, although sensitivity of testing was found to be higher in symptomatic patients and those in the early stage from onset, compared to asymptomatic patients and those in

**Table 2**  
Concordance between the antigen test results between NP and AN sampling.

Antigen kit	Sample site	Sensitivity (95% CI), n/N	Specificity (95% CI), n/N	Positive concordance rate of AN to NP sampling (95% CI), n/N	Negative concordance rate of AN to NP sampling (95% CI), n/N
Espline	AN	0.81 (0.64–0.93), 26/32	1.00 (0.96–1.00), 96/96	0.87 (0.69–0.96), 26/30	1.00 (0.96–1.00), 98/98
	NP	0.94 (0.79–0.99), 30/32	1.00 (0.96–1.00), 96/96		
Lumipulse G1200	AN	0.91 (0.75–0.98), 29/32	1.00 (0.96–1.00), 96/96	0.94 (0.79–0.99), 29/31	1.00 (0.96–1.00), 97/97
	NP	0.97 (0.84–1.00), 31/32	1.00 (0.96–1.00), 96/96		
Lumipulse L2400	AN	0.91 (0.75–0.98), 29/32	1.00 (0.96–1.00), 96/96	0.85 (0.69–0.95), 29/34	1.00 (0.96–1.00), 94/94
	NP	0.97 (0.84–1.00), 31/32	0.97 (0.91–0.99), 93/96		

Abbreviations: CI, confidence interval; AN, anterior nasal; NP, nasal pharynx.



**Fig. 1.** Comparison of antigen levels of Lumipulse G1200 and L2400 SARS-CoV-2 Ag tests between anterior nasal (AN) and nasopharyngeal (NP) sampling. Box plot shows the median Lumipulse antigen value with the interquartile range. Wilcoxon rank-sum test was used to compare the antigens levels between AN and NP sampling. The dotted lines show the positive cutoff values. Abbreviations: Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2.

the late stage from onset [22]. A similar tendency was found for the rapid antigen testing kits used in our studies [17,23]. A statistical evaluation of the effects of obesity and upper respiratory symptoms on the test accuracy of ESP was not possible due to the small sample size of our study, and a future study with a larger sample size is warranted.

There were several limitations of this study. First, all included patients were symptomatic, and their viral loads were high possibly because these patients were in the early stage of onset. Since it has been reported that SARS-CoV-2 is difficult to detect in asymptomatic patients in the early stages of infection by AN sampling, the test accuracy found our study may not be directly applicable to asymptomatic patients [24]. However, since testing of close contacts is expected to show high viral shedding like that seen in symptomatic patients, frequent testing after exposure to a COVID-19 patient is expected to have some significance in detecting the early stages of the disease. In addition, although our study included inpatients and outpatients, we think that most of the patients had mild diseases and there were few differences between patients in terms of disease severity. Second, the patients in our study were predominantly middle-aged and could be expected to do satisfactory self-sampling. However, children and the elderly may not be able to perform adequate self-sampling. Therefore, it might be necessary to

differentiate the patient backgrounds to determine the appropriate collection method. Third, the antigen tests in this study used specimens diluted in transport media. To minimize the effect, 1 ml of media was used, whereas the package insert used 200  $\mu$ L of the reaction solution. The results were somewhat disadvantageous for the qualitative antigen test. Even so, antigen qualitative testing using AN samples was able to meet the minimum WHO performance criteria for rapid antigen testing [12]. Finally, although we calculated the sample size for the primary outcome, the sample size might have been insufficient to analyze the factors affecting the concordance between AN sampling and NP sampling. A future study with a larger sample size is warranted to analyze the impact of various factors on the concordance between the two sampling approaches.

In conclusion, the ESP, LUMI, and LUMI-P demonstrated practical diagnostic accuracy for AN sampling compared to NP sampling. There was no significant factor affecting the concordance between AN and NP sampling for ESP, LUMI, and LUMI-P. However, testing accuracy of AN sampling for ESP might be negatively influenced by obesity, while it might be improved among patients with upper respiratory symptoms. A future study with a larger sample size is warranted to assess the factors affecting the test accuracy of different sampling methods for rapid

**Table 3**

Factors affecting the concordance of results for the Espline SARS-CoV-2 Ag test between AN and NP sampling among confirmed COVID-19 patients (N = 32).

Variable	Concordant results between AN and NP sampling, proportion (n/N)	Disconcordant results between AN and NP sampling, proportion (n/N)	p-value
<b>Basic demographics</b>			
Female sex	0.69 (18/26)	0.83 (5/6)	0.648
Age ≥65 years	0.35 (9/26)	0.17 (1/6)	0.637
Self-sampling	0.69 (18/26)	0.40 (2/5)	0.317
BMI >25 kg/m <sup>2</sup>	0.35 (9/26)	0.83 (5/6)	0.064
Time from onset to testing, ≤ 5 days	0.65 (17/26)	0.33 (2/6)	0.194
<b>Symptoms at sample collection</b>			
Fever ≥37.5 °C	0.69 (18/26)	0.50 (3/6)	0.390
Fatigue	0.42 (11/26)	0.33 (2/6)	1.000
Upper respiratory symptoms	0.42 (11/26)	0 (0/6)	0.071
Lower respiratory symptoms	0.50 (13/26)	0.33 (2/6)	0.659
Smell or taste dysfunction	0.31 (8/26)	0.17 (1/6)	0.648

Abbreviations: COVID-19, coronavirus disease; AN, anterior nasal; NP, nasal pharynx; BMI, Body Mass Index.

antigen testing.

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### Declaration of competing interest

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### Appendix A. Supplementary data

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