



# The use of saliva specimens for detection of influenza A and B viruses by rapid influenza diagnostic tests



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## ABSTRACT

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**Background and objectives:** Diagnostic tests for influenza infection commonly use nasopharyngeal swabs (NPS) even though these are invasive to obtain. As an alternative specimen, we evaluated the diagnostic usefulness of saliva samples with rapid influenza diagnostic tests (RIDTs).

**Study design:** Both NPS and saliva samples were collected from 385 influenza suspected patients and analyzed using Sofia Influenza A + B Fluorescence Immunoassay (Quidel Corporation, San Diego, CA, USA), ichroma TRIAS Influenza A + B (Boditech, Chuncheon, Korea), SD Bioline Influenza Ag (Standard Diagnostic, Yongin, Korea), BinaxNOW Influenza A/B antigen kit (Alere Inc., Waltham, MA, USA), and real-time reverse transcriptase PCR (RT-PCR).

**Results:** Of the 385 patients, 31.2% (120/385) were positive for influenza A, and 7.5% (29/385) were positive for influenza B virus with saliva or NPS by RT-PCR. The diagnostic sensitivity was slightly higher in NPS than in saliva samples for both influenza A and B by all of the four RIDTs. The diagnostic sensitivities of Sofia and ichroma TRIAS were significantly superior to those of the other conventional influenza RIDTs with both types of sample. The sensitivities of Sofia and ichroma TRIAS with saliva specimens were comparable to the sensitivities of the other two conventional RIDTs with NPS specimens. The simultaneous use of saliva and NPS samples exhibited improved sensitivity from 10.0% to 13.3% for influenza A and from 10.3% to 17.2% for influenza B compared to using NPS alone.

**Conclusions:** This study demonstrates that saliva is a useful specimen for influenza detection, and that the combination of saliva and NPS could improve the sensitivities of influenza RIDTs.

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## 1. Background and objectives

Rapid and accurate diagnosis of influenza infection is important for proper treatment, reducing unnecessary testing, and implementation of infection control measures. For this reason, various diagnostic methods have been developed and used for the detection of influenza, such as virus cultures, reverse transcriptase-polymerase chain reactions (RT-PCR), and rapid influenza diagnostic tests (RIDTs). Reverse transcriptase-polymerase chain reaction (RT-PCR) is one of the most sensitive methods for influenza detection and is considered the reference method. In addition, RIDTs have been commonly used due to their speed in test results and ease of use, but commercially available RIDTs have been reported to demonstrate a broad range of sensitivities

from 11% to 80% (Hurt et al., 2007; Uyeki et al., 2009; Chartrand et al., 2012). Recently developed RIDTs employing europium dye for immunofluorescence assays, such as the Sofia Influenza A + B Fluorescence Immunoassay, have shown enhanced sensitivity ranging from 75% to 91% for influenza A and 50% to 77% for influenza B (Hazelton et al., 2015; Lee et al., 2012; Dunn et al., 2014).

For influenza virus identification, nasopharyngeal swab (NPS) samples have been traditionally used as the most practical specimen with a high concentration of virus and detection sensitivity (Covalciuc et al., 1999). However, NPS specimen collection can be physically challenging, especially for pediatric patients, due to its invasive and uncomfortable procedure. With the advent of easier specimen collection methods for influenza diagnosis, saliva has been introduced. When assessed with RT-PCR, saliva exhibited an overall concordance of results over 95% compared to NPS specimens (Sueki et al., 2016; Bilder et al., 2011). Saliva specimens are less invasive to collect than other specimens and may be valuable for influenza detection. The purpose of this study was to compare the clinical performance between saliva and NPS specimens in four

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commercially available RIDTs and RT-PCR. Both the Sofia Influenza A + B Fluorescence Immunoassay and ichroma TRIAS Influenza A + B (Boditech, Chuncheon, Korea) adopt the europium-based fluorescence immunoassay with a digital reader system, while the other RIDTs are based on the conventional immunochromatographic principle. We also evaluated the incremental diagnostic value of saliva when used in conjunction with NPS.

## 2. Study design

### 2.1. Sample collection and preparation

NPS and saliva were collected simultaneously from 385 patients presenting flu-like symptoms at Korea University Guro Hospital from December 2014 to April 2015. Flu-like symptoms were defined as a body temperature of 37.8 °C or higher with one or more respiratory symptoms, including cough or sore throat. All specimens were obtained within 48 h post onset of illness. All patients provided informed consent under the protocol for human use approved by the Human Use Ethical Committee, Korea University Guro Hospital. NPSs were collected with flocked swabs (Copan Diagnostics, Brescia, Italy) from each patient and transported in 1.5 mL of viral transport medium (UTM viral transport medium, Copan Diagnostics). Saliva samples were collected into sterile plastic containers. Obtained NPS and saliva samples were stored at 4 °C, transported to the laboratory within 24 h of collection, and stored at –80 °C until analysis.

### 2.2. Molecular assays

For molecular diagnosis, a custom real-time RT-PCR assay was performed as previously described (Jang et al., 2015). RNA was extracted from 140 µL of nasopharyngeal specimens in the viral transport medium and saliva specimens using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany). We used previously reported primers (FluA-F 5'-AGATGAGTCTTCTAACCGAGGTCTG-3', FluA-R 5'-TGACAGRATYGGTCTTGTCTTTAGCCAYTCCA-3', FluA-probe 5'-TCAGGCCCTCAAGCCGAG-3', FluB –F 5'-TACACAGCAAAAAGACCC-3', FluB-R 5'-TCCACTCCCTTCTCCCC-3', FluB-probe (5'-ACACCCAGACCAGATGA-3') for influenza A and B (Jang et al., 2015). Real time RT-PCR procedures were performed with the commercially available DiaStar onestep multiplex qRT-PCR kit (SolGent, Daejeon, Korea). Real time RT-PCR was conducted with a final reaction volume of 25 µL, which included 2.5 µL of isolated viral RNA, 0.1 µM of forward and reverse primers, and 0.1 µM of probe. Real time RT-PCR was performed with a real-time thermocycler CFX96 (Bio-Rad, Hercules, CA, USA) under the following conditions: reverse transcription at 50 °C for 20 min, initial denaturation at 95 °C for 10 min, and 45 cycles of 95 °C for 15 s and 60 °C for 60 s. Ct values under 40 were considered positive.

### 2.3. RIDTs

All samples were concurrently analyzed with four commercially available RIDTs, the Sofia Influenza A + B Fluorescence Immunoassay (Quidel Corporation, San Diego, CA, USA), ichroma TRIAS Influenza A + B (Boditech, Chuncheon, Korea), SD Bioline Influenza Ag (Standard Diagnostic, Yonggjin, Korea), and BinaxNOW Influenza A/B antigen kit (Alere Inc., Waltham, MA, USA). All tests involving NPS were performed according to the manufacturers' instructions. For the salivary specimens, all tests were carried out with protocols similar to the ones used for the NPS specimens.

Briefly, a volume of 300 µL of nasopharyngeal or saliva specimens for the Sofia Influenza A + B Fluorescence Immunoassay and ichroma TRIAS Influenza A + B and 50 µL of nasopharyngeal or saliva specimens for the SD Bioline Influenza Ag and BinaxNOW Influenza

**Table 1**

Characteristics of patients with suspected influenza infection.

Characteristics	Total	Influenza A	Influenza B	Negative
Number of patients (%)	385 (100%)	120 (31.2%)	29 (7.5%)	236 (61.3%)
Age (years)				
Median	46	41	36	46
Range	6–97	15–97	16–79	6–93
Sex (%)				
Male	179 (46.5%)	47 (39.2%)	16 (55.2%)	116 (49.2%)
Female	206 (53.5%)	73 (60.8%)	13 (44.8%)	120 (50.8%)

A/B antigen kit were mixed with an equal volume of reagent solution. The reaction mixture was then inserted into the test kit. The results were interpreted 15 min later. In the Sofia Influenza A + B Fluorescence Immunoassay and ichroma TRIAS Influenza A + B, the results were automatically obtained with a portable fluorescence analyzer.

### 2.4. Data analysis

The sensitivity and specificity of RIDTs for the detection of influenza virus with NPS and saliva specimens were calculated by considering any positive RT-PCR results from either NPS or saliva specimens as true positives. The parameters were expressed as 95% confidence interval (CI). Sensitivities between NPS and saliva were compared using the  $\chi^2$  test or Fisher's exact test. Statistical significance was determined at a *p*-value < 0.05. Agreement of results between the NPS and saliva specimens was assessed by the kappa coefficient, and the strength of agreement was defined as follows: Cohen's kappa coefficient (K): <0 = poor, 0–0.2 = slight, 0.21–0.4 = fair, 0.41–0.6 = moderate, 0.61–0.8 = substantial, and 0.81–1 = almost perfect (Landis and Koch, 1977). The incremental diagnostic value of saliva for RT-PCR was calculated as a ratio of the number of positive results obtained from only saliva samples to the number of positive results from NPS. In RIDTs, the incremental value was decided as the increased percentage of sensitivity when considering positive results from either NPS or saliva as positive compared to using NPS alone. All data were analyzed using SPSS version 21.0 (SPSS, Chicago, IL, USA).

## 3. Results

Pairs of NPS and saliva samples were collected from a total of 385 patients. The median age of patients was 46 years (ranged from 6 to 97 years), and the percentages of male and female patients were 46.5% (179/385) and 53.5% (206/385), respectively (Table 1).

Of the 385 paired NPS and saliva samples, 31.2% (120/385) were positive for influenza A virus and 7.5% (29/385) were positive for the influenza B virus when any positive RT-PCR results from either NPS or saliva specimens were considered as a true positive (Table 1). The positivity rates of RT-PCR with the NPS samples were significantly higher than those of the saliva samples for influenza A (94.2% (113/120) vs. 85.0% (102/120), *p* < 0.01) and influenza B detection (93.1% (27/29) vs. 69.0% (20/29), *p* < 0.01) (Table 2). The concordance rates between the NPS and saliva samples by RT-PCR were 93.5% (360/385) for influenza A and 97.1% (374/385) for influenza B.

Compared to RT-PCR, the sensitivities of Sofia Influenza A + B Fluorescence Immunoassay, ichroma TRIAS Influenza A + B, SD Bioline Influenza Ag, and BinaxNOW Influenza A/B antigen kit for detection of influenza A virus were 74.2% (*n* = 89/120, 95% CI 65.4–81.7), 74.2% (*n* = 89/120, 95% CI 65.4–81.7), 63.3% (*n* = 76/120, 95% CI 54.1–71.9), and 60.8% (*n* = 73/120, 95% CI 51.5–69.6) for the NPS specimens, respectively, and 59.2% (*n* = 71/120, 95% CI 49.8–68.1), 59.2% (*n* = 71/120, 95% CI 49.8–68.1), 30.8% (*n* = 37/120,

**Table 2**

Comparison of RT-PCR results for influenza virus detection between nasopharyngeal swabs and saliva samples.

Influenza type	No. of positive					Kappa statistic (95% CI)	% Increase using saliva (95% CI)
	Either NPS or Saliva	NPS (%)	Saliva (%)	Only NPS (%)	Only Saliva (%)		
A	120	113 (94.2%)	102 (85.0%)	18 (15.0%)	7 (5.8%)	0.84 (0.78–0.90)	6.2 (3.0–12.2)
B	29	27 (93.1%)	20 (69.0%)	9 (31.0%)	2 (6.9%)	0.75 (0.61–0.90)	7.4 (2.1–23.4)

NPS, nasopharyngeal swabs; CI, confidence interval.

95% CI 22.7–39.9), and 30.0% ( $n = 36/120$ , 95% CI 22.0–39.0) for the saliva specimens. For influenza B virus, the sensitivities were 75.9% ( $n = 22/29$ , 95% CI 56.5–89.7), 75.9% ( $n = 22/29$ , 95% CI 56.5–89.7), 75.9% ( $n = 22/29$ , 95% CI 56.5–89.7), and 58.6% ( $n = 17/29$ , 95% CI 38.9–76.5) for the NPS specimens, respectively, and 65.5% ( $n = 19/29$ , 95% CI 45.7–82.1), 62.1% ( $n = 18/29$ , 95% CI 42.3–79.3), 41.4% ( $n = 12/29$ , 95% CI 23.5–61.1), and 31.0% ( $n = 9/29$ , 95% CI 15.3–50.8) for the saliva specimens (Table 3). Regarding the specimens, the sensitivities of RIDTs for both influenza A and B were more sensitive when tested with NPS than saliva (all  $p < 0.01$ ). Meanwhile, the strength of agreement between the specimens for RIDTs varied. The Sofia Influenza A+B Fluorescence Immunoassay and ichroma TRIAS Influenza A+B exhibited moderate agreement for both influenza A ( $\kappa = 0.60$  and  $\kappa = 0.60$ , respectively) and B ( $\kappa = 0.60$  and  $\kappa = 0.53$ , respectively). SD Bioline Influenza Ag presented a fair strength of agreement for both influenza A ( $\kappa = 0.36$ ) and B ( $\kappa = 0.40$ ), while the BinaxNOW Influenza A/B antigen kit had a fair agreement for influenza A ( $\kappa = 0.35$ ), but moderate agreement for influenza B ( $\kappa = 0.41$ ) (Table 3).

The specificities of all four RIDTs for detecting influenza A virus with NPS compared to RT-PCR results were 100% ( $n = 265/265$ , 95% CI 98.6–100). The specificity of Sofia Influenza A+B Fluorescence Immunoassay, ichroma TRIAS Influenza A+B, SD Bioline Influenza Ag, and BinaxNOW Influenza A/B antigen kit RIDTs for detecting the influenza A virus with saliva was 99.6% ( $n = 264/265$ , 95% CI 97.9–100), 100% ( $n = 265/265$ , 95% CI 98.6–100), 100% ( $n = 265/265$ , 95% CI 98.6–100) and 99.2% ( $n = 263/265$ , 95% CI 97.3–99.9), respectively (Table 3). For detection of influenza B virus, the specificities of RIDTs with NPS were 99.7% ( $n = 355/356$ , 95% CI 98.4–100), while that of SD Bioline Influenza Ag was 99.2% ( $n = 353/356$ , 95% CI 97.6–99.8). When tested with saliva, the specificities of RIDTs for detecting influenza B virus of Sofia Influenza A+B Fluorescence Immunoassay, ichroma TRIAS Influenza A+B, SD Bioline Influenza Ag, and BinaxNOW Influenza A/B antigen kit were 99.2% ( $n = 353/356$ , 95% CI 97.6–99.8), 99.7% ( $n = 355/356$ , 95% CI 98.4–100), 98.6% ( $n = 351/356$ , 95% CI 96.8–99.5), and 99.7% ( $n = 355/356$ , 95% CI 98.4–100), respectively (Table 3).

The use of saliva increased the number of samples detected with RT-PCR for influenza A and B by 6.2% ( $n = 7/113$ , 95% CI 3.0–12.2) and 7.4% ( $n = 2/27$ , 95% CI 2.1–23.4), respectively (Table 2). Moreover, when results of either NPS or saliva were considered positive, the use of saliva samples increased the sensitivities of RIDTs and ranged from 10.0% ( $n = 12/120$ , 95% CI 5.8–16.7) to 13.3% ( $n = 16/120$ , 95% CI 8.4–20.6) for influenza A and 10.3% ( $n = 3/29$ , 95% CI 3.6–26.4) to 17.2% ( $n = 5/29$ , 95% CI 7.6–34.6) for influenza B compared to using NPS alone (Table 3).

#### 4. Discussion

To our knowledge, this is the first study to evaluate saliva for influenza identification with various RIDTs. To date, all studies comparing NPS and saliva specimens have been conducted with RT-PCR (Sueki et al., 2016; Bilder et al., 2011; Robinson et al., 2008), prob-

ably because RT-PCR is the most sensitive and specific diagnostic method for influenza infection. Sueki et al. evaluated saliva as the diagnostic material for influenza virus detection with RT-PCR, and the overall concordance of results with NPS were 95.8% (Sueki et al., 2016). In contrast, although the study included only a small number of patients with influenza infection, Robinson et al. reported that none of the patients with influenza virus detected in NPS samples were positive with saliva samples when tested with RT-PCR (Jang et al., 2015). In our study, a high degree of agreement of results was obtained between NPS and saliva when assayed with RT-PCR for both influenza A and B. Our estimates of the concordance rate between NPS and saliva were within the range of the previously reported results and were slightly lower for influenza A (93.5%) but slightly higher for influenza B (97.1%) (Sueki et al., 2016).

The diagnostic yields of the saliva specimens, including sensitivity and agreement with NPS, were variable depending on which RIDT was used. As expected, of the evaluated RIDTs, two fluorescence immunoassays with a digital reader system, Sofia Influenza A+B Fluorescence Immunoassay and ichroma TRIAS Influenza A+B, yielded higher sensitivity with both NPS and saliva than the two traditional RIDTs.

Regarding the specimens, the sensitivities of RIDTs for both influenza A and B were significantly higher when tested with NPS versus saliva. Nonetheless, the sensitivities of Sofia Influenza A+B Fluorescence Immunoassay and ichroma TRIAS Influenza A+B with saliva specimens were comparable to those of SD Bioline Influenza Ag and the BinaxNOW Influenza A/B antigen kit with NPS specimens. In the case of influenza B identification, the Sofia Influenza A+B Fluorescence Immunoassay tested with saliva yielded higher sensitivity compared to the BinaxNOW Influenza A/B antigen kit tested with NPS. Considering the agreement of results between NPS and saliva, a fair to moderate strength of agreement was presented, and the Sofia Influenza A+B Fluorescence Immunoassay and ichroma TRIAS Influenza A+B displayed the highest kappa coefficient of 0.60 for influenza A and the Sofia Influenza A+B Fluorescence Immunoassay presented the highest kappa coefficient of 0.60 for influenza B.

The incremental value of saliva specimens for influenza detection was observed with both RT-PCR and RIDTs. For better diagnostic yields, previous studies suggested sampling oropharyngeal swabs in conjunction with NPS and reported an incremental range of 7.1% to 8.8% using oropharyngeal swabs for respiratory virus detection with RT-PCR (Ali et al., 2015; Hammitt et al., 2011). When testing influenza virus, the added value of the oropharyngeal swabs was 22% (Hammitt et al., 2011). Since saliva specimens could improve the sensitivity from 6.2% to 7.4% based on RT-PCR results compared to NPS alone, saliva might be less useful in RT-PCR. On the other hand, a more profound incremental value of saliva was observed with RIDTs, improving the influenza detection of RIDTs by 10.0% to 17.2% and achieving a sensitivity range of 70.8% ( $n = 85/120$ , 95% CI 61.8–78.8) to 87.5% ( $n = 105/120$ , 95% CI 80.2–92.8) for influenza A and 69.0% ( $n = 20/29$ , 95% CI 49.2–84.7) to 93.1% ( $n = 27/29$ , 95% CI 77.2–98.2) for influenza B. It is noteworthy

**Table 3**  
Comparison of rapid influenza diagnostic test results between nasopharyngeal swabs and saliva samples

Influenzatype	RIDTs	Either NPS or Saliva Sensitivity (95% CI)	% Increase using Saliva (95% CI)	NPS Sensitivity (95% CI)	NPS Specificity (95% CI)	Saliva Sensitivity (95% CI)	Saliva Specificity (95% CI)	p-value	Kappa statistic (95% CI)
A	Sofia Influenza A + B Fluorescence Immunoassay	105/120, 87.5% (80.2–92.8)	13.3% (8.4–20.6)	89/120, 74.2% (65.4–81.7)	265/265, 100% (98.6–100)	71/120, 59.2% (49.8–68.1)	264/265, 99.6% (97.9–100)	<0.01	0.60 (0.50–0.70)
	ichroma TRIAS Influenza A + B	104/120, 86.7% (79.3–92.2)	12.5% (7.7–19.6)	89/120, 74.2% (65.4–81.7)	265/265, 100% (98.6–100)	71/120, 59.2% (49.8–68.1)	265/265, 100% (98.6–100)	<0.01	0.60 (0.53–0.69)
	SD Bioline Influenza Ag	88/120, 73.3% (64.5–81.0)	10.0% (5.8–16.7)	76/120, 63.3% (54.1–71.9)	265/265, 100% (98.6–100)	37/120, 30.8% (22.7–39.9)	265/265, 100% (98.6–100)	<0.01	0.36 (0.22–0.50)
	BinaxNOW Influenza A/B antigen kit	85/120, 70.8% (61.8–78.8)	10.0% (5.8–16.7)	73/120, 60.8% (51.5–69.6)	265/265, 100% (98.6–100)	36/120, 30.0% (22.0–39.0)	263/265, 99.2% (97.3–99.9)	<0.01	0.35 (0.20–0.50)
	Sofia Influenza A + B Fluorescence Immunoassay	27/29, 93.1% (77.2–99.2)	17.2% (7.6–34.6)	22/29, 75.9% (56.5–89.7)	355/356, 99.7% (98.4–100)	19/29, 65.5% (45.7–82.1)	353/356, 99.2% (97.6–99.8)	<0.01	0.60 (0.41–0.79)
	ichroma TRIAS Influenza A + B	26/29, 89.7% (72.7–97.8)	13.8% (5.5–30.6)	22/29, 75.9% (56.5–89.7)	355/356, 99.7% (98.4–100)	18/29, 62.1% (42.3–79.3)	355/356, 99.7% (98.4–100)	<0.01	0.53 (0.39–0.69)
B	SD Bioline Influenza Ag	25/29, 86.2% (68.3–96.1)	10.3% (3.6–26.4)	22/29, 75.9% (56.5–89.7)	353/356, 99.2% (97.6–99.8)	12/29, 41.4% (23.5–61.1)	351/356, 98.6% (96.8–99.5)	<0.01	0.40 (0.16–0.63)
	BinaxNOW Influenza A/B antigen kit	20/29, 69.0% (49.2–84.7)	10.3% (3.6–26.4)	17/29, 58.6% (38.9–76.5)	355/356, 99.7% (98.4–100)	9/29, 31.0% (15.3–50.8)	355/356, 99.7% (98.4–100)	<0.01	0.41 (0.13–0.69)

RIDTs, rapid influenza diagnostic tests; NPS, nasopharyngeal swabs; CI, confidence interval.

thy that the incremental value was observed with all RIDTs that had been assessed. The main drawback of using an RIDT as the diagnostic method for influenza is its modest and highly variable sensitivity (Chartrand et al., 2012; McMullen et al., 2016). Therefore, our results suggest that assessing paired saliva and NPS could be used in place of NPS alone for better diagnostic yields.

It is expected that PCR is more sensitive than RIDT in influenza detection. The quality of NPS would have a stronger influence on the sensitivity of RIDT than PCR. For saliva specimens, which may not be expected to have high viral concentrations, these would yield lower sensitivities in both tests. Therefore, if the NPS were optimally collected with enough numbers of influenza virus infected cells or exudates, the difference of sensitivities between RIDTs and PCR may not be high.

In conclusion, this study showed that saliva could be a valuable specimen for influenza detection when used with highly sensitive rapid diagnostic kits. When diagnosing influenza with saliva specimens, RT-PCR yields the highest degree of agreement with NPS sample results. Among RIDTs, the Sofia Influenza A+B Fluorescence Immunoassay and ichroma TRIAS Influenza A+B are preferred assays and provide comparable diagnostic yields to other RIDTs tested with NPS. In addition, we found that combining saliva with NPS had an incremental value over NPS alone by increasing the sensitivities in both RT-PCR and RIDTs.

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### Conflict of interest

No conflicts of interest to declare.

### Ethical approval

This study was approved by the Human Use Ethical Committee at Korea University Guro Hospital (MD 14022-001).

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