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Comparison of two new generation influenza rapid diagnostic tests with instrument-based digital readout systems for influenza virus detection

S.-W. Ryu[a†], J.-H. Lee[b†], J. Kim[c], M.-A. Jang[c], J.-H. Nam[c], M.-S. Byoun[c] and C. S. Lim[c]

[a]Department of Laboratory Medicine, School of Medicine, Kangwon National University, Chuncheon, Korea; [b]Department of Laboratory Medicine, Osan Hankook General Hospital, Osan, Korea; [c]Department of Laboratory Medicine, College of Medicine, Korea University, Seoul, Korea

ABSTRACT

Introduction: Influenza rapid diagnostic tests (RDTs) have been developed to supply scientists with more sensitive and specific techniques. Newly developed digital reader-based techniques require test evaluations before their clinical application.

Methods: Two types of digital influenza RDTs using a digital readout system and one conventional RDT were compared using 314 nasopharyngeal swabs of influenza. The swabs originated from symptomatic individuals suspected of influenza infection, and the presence of influenza was confirmed with influenza real-time polymerase chain reaction (PCR) testing and influenza subtyping. Methods were the Sofia® Influenza A + B Fluorescence Immunoassay (FIA), which uses a portable fluorescence analyser, the BD Veritor™ System Flu A + B, which uses a colorimetric immunochromatographic method with a reflectance-based measurement digital device, and the SD Bioline assay, which is based on a traditional immunochromatographic method.

Results: The Sofia® Influenza A + B system, the BD Veritor™ System Flu A + B and the SD Bioline assay showed sensitivities in relative real-time PCR results of 74.2, 73.0 and 53.9%, respectively, for influenza A, and 82.5, 72.8 and 71.0%, respectively, for influenza B. All three RDTs showed 100% specificities for influenza A and influenza B. The Sofia® Influenza A + B Fluorescence Immunoassay showed sensitive and specific results for the detection of influenza B in contrast to the BD Veritor™ System Flu A + B. The two digital RDTs showed higher sensitivity and specificity than the conventional RDT in the detection of the influenza H3 subtype.

Conclusions: Digital-based readout systems for the detection of the influenza virus can be applied for more sensitive diagnosis in clinical settings than conventional RDTs.

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Introduction

Due to high morbidity and mortality, influenza causes serious public health concerns worldwide. Accurate and rapid diagnosis of influenza infection is essential for appropriate patient management and anti-influenza therapy. For ideal diagnosis of influenza, the virus can be isolated in tissue cultures or chick embryos within 48–72 h following inoculation. Most commonly, rapid tests that detect viral antigens by means of immunologic or enzymatic techniques have been established in many clinical laboratories. Influenza rapid diagnostic tests (RDTs) are convenient and fast for patients with clinically suspected influenza. A major limitation of RDTs; however, is the broad range of sensitivity (19.7–82%) associated with the tests.[1] Variation in RDT sensitivity is due to reactivity differences of RDTs in terms of antibodies to influenza antigens and methods to detect antigen–antibody reaction, as well as patient age, specimen type, strain of virus and mean time of sample after the onset date of illness.[1,2]

Recently, influenza RDTs equipped with digital reader systems have been introduced and evaluated for comparison of detection sensitivity.[2,3] The Sofia® Influenza A + B Fluorescence Immunoassay (Sofia; Quidel Corp., San Diego, CA, USA) detects influenza A and B viruses using immunofluorescence technology with europium dye, and is interpreted with a portable fluorescence automatic reader. The BD Veritor™ System Flu A + B (Veritor; BD Diagnostics, Sparks, MD, USA) utilises advanced particle technology in an immunochromatographic assay, which is provided with an instrument-based digital readout system. This digital immunoassay system is hypothesised to reduce operator variability, false negativity by enhanced sensitivity and false positivity by reducing nonspecific reactions.

The aim of this study is to evaluate the performance of these two newly introduced influenza RDTs with digital readout systems, the Sofia® Influenza A + B Fluorescence Immunoassay (FIA) and the BD Veritor™ System Flu A + B (Veritor; BD Diagnostics, Sparks, MD, USA), and one

CONTACT C. S. Lim malarim@korea.ac.kr
[†]Both authors contributed equally in performing this study and writing the article.

traditional commercial RDT, the SD BIOLINE Influenza Antigen Test (Standard Diagnostics, Yongin, Republic of Korea).

Materials and methods

Specimen collection and preparation

From January 2014 to February 2015, nasopharyngeal swabs (NS) were collected from 314 patients showing influenza-like symptoms at the Korea University Guro Hospital in Seoul, Korea. The sampling time was less than 48 h after the onset point of symptoms for all patients. Patient samples were transported in vials containing three milliliters (mL) of viral transport medium, and were immediately used for real-time reverse transcription polymerase chain reaction (RT-PCR) testing for the influenza virus. The remaining specimens were then cryopreserved at –80 °C until influenza rapid antigen testing was conducted. All of the specimens underwent a single freeze-thaw cycle. Each of the three influenza RDTs and real-time RT-PCR tests were carried out according to the manufacturers' instructions. The mean age of patients was 30.4 years, ranging from two months to 90 years. There were a total of 163 male (*M*) and 151 female (*F*) patients (the *M*:*F* ratio was 1.03:1) (Table 1). This study was approved by the Institutional Research Ethics Board of the Korea University Guro Hospital (approval No.: KUGH-10230).

Three influenza rapid diagnostic tests

Sofia Influenza A+B Fluorescence Immunoassay (Sofia)

The Sofia Influenza A + B FIA (Quidel, San Diego, CA) uses a lateral flow design based on immunofluorescence technology to enhance detection sensitivity.[5] For each test, a volume of 300 µL of nasopharyngeal specimen in viral transport medium (VTM) was added on the Sofia nitrocellulose cassette, then approximately 15 min to allow the reaction to occur. The test cassette was inserted into the portable fluorescence reader, and the results were automatically printed within one minute.

BD Veritor™ System Flu A+B (Veritor)

The BD Veritor™ System Flu A + B assay (BD Diagnostics, Sparks, MD, USA) uses a colorimetric immunochromatographic method to detect influenza antigens, which is similar to the method of traditional RDTs, with a digital reader.[3] A digital reader is a portable electronic device, which uses a reflectance-based measurement to analyse the line signal intensities of the test strip. The BD Veritor™ System Flu A + B uses 300 µl of nasopharyngeal specimen which is VTM-transferred to an RV reagent C tube and thoroughly mixed. For analysis, three drops of the processed sample were dispensed into the sample well of the test kit device. After 10 min, the test kit device was inserted into the BD Veritor System reader, and the instrument digitally displayed the test results. The instrument read time was 10 s.

SD BIOLINE Influenza Antigen rapid test (Bioline)

The SD BIOLINE Influenza Antigen rapid test (Standard Diagnostics, Yongin, Korea) is a chromatographic immunoassay for the qualitative detection of influenza virus type A and type B using embedded mouse monoclonal anti-influenza A and anti-influenza B antibodies in the test strip. In brief, the process for analysis involved 50 µL of nasopharyngeal specimen in VTM, which was mixed with the same volume of reagent solution. The test strip was inserted into a tube containing a total volume of 100 µL of the reaction mixture. Test results were visually examined and interpreted after approximately 15 min. Basic characteristics of the three types of RDTs are summarised in Table 2.

Real-time PCR for influenza detection

For an in-house method, influenza RT-PCR viral RNAs were extracted with the QIAamp® Viral RNA Mini Kit (Qiagen, Hilden, Germany) from 140 µL of the respiratory specimen. A one-step, real-time RT-PCR method

Table 1. Enrolled patient characteristics.

Characteristics	Total	Influenza A	Influenza B	Negative
No. of patients	314	89	103	122
Mean age (range)	30.4 (2 mo-90 yr)	32.9 (2 mo-90 yr)	23.3 (4 mo-87 yr)	34.5 (4 mo-87 yr)
Males/Females	163/151	44/45	60/43	59/63

Table 2. Characteristics of each rapid diagnostic test for influenza virus detection.

Rapid test kits	Assay volume (µL)	Assay time (min)	Identification of influenza A/B	Recommended specimen	Interpretation
SD BIOLINE Influenza Antigen test	100	15	Yes	NPW, NPA, NPS, LNS, TS, BAL	Eye
Sofia Influenza A+B Fluorescence Immunoassay	300	15	Yes	NW, NPA, NPS	Fluorescence reader
BD Veritor™ System Flu A+B	300	10	Yes	NPW, NPA, NPS	Optical reader

Abbreviations: NPW, nasopharyngeal wash; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; LNS, lower nasal swab; TS, throat swab; BAL, bronchoalveolar lavage.

Table 3. In-house real-time PCR primer and probe sequences for influenza A and influenza B.

Primer/Probe	Concentration	Purification	Sequence
FLU-A-Forward	200 nmole	PAGE	AGATGAGTCTTCTAACCGAGGTCG
FLU-A-Reverse	200 nmole	PAGE	TGACAGRATYGGTCTTGTCTTTAGCCAYTCCA
FLU-A-Probe	200 nmole	PAGE	[5FAM]TCAGGCCCCCTCAAAGCCGAG[3BHQ1]
FLU-B-Forward	200 nmole	PAGE	TACACAGCAAAAAGACCC
FLU-B-Reverse	200 nmole	PAGE	TCCACTCCCTTTCTCCCC
FLU-B-Probe	200 nmole	PAGE	[5HEX]ACACCCCCAGACCAGATGA[3BHQ1]
IC-Forward	200 nmole	PAGE	GAAGGTGAAGGTCGGAGT
IC-Reverse	200 nmole	PAGE	GAAGATGGTGATGGGATTTC
IC-Probe	200 nmole	PAGE	[5CY5]CAAGCTTCCCGTTCTCAGCC[3BHQ2]

Abbreviations: FLU-A, influenza A; FLU-B, influenza B; IC, internal control; PAGE, polyacrylamide gel electrophoresis.

was performed according to guidelines in the work of van Elden et al., with minor modifications.[5] In brief, each tube contained a 25-µL reaction mix that included 2.5 µL of isolated viral RNA, 0.1 µM forward and reverse primer and a 0.1 µM probe. The real-time PCR primer and probe are described in Table 3. TaqMan amplification and detection were performed with a real-time thermocycler CFX96 (Bio-Rad, Hercules, CA, USA). Thermocycling conditions were as follows: reverse transcription at 50 °C for 20 min, and then initial denaturation at 95 °C for 10 min, followed by 45 cycles at 95 °C for 15 s and at 60 °C for 60 s.

Influenza subtyping

In parallel with the real-time RT-PCR assay, the Seeplex Influenza A/B OneStep Typing (Seegene, Seoul, Republic of Korea) was performed to subtype the influenza A virus. The assay is able to detect influenza A and B, and to identify three subtypes of influenza A (H1, H3 and H1N1/2009). Reverse transcription and PCR were performed on the GeneAmp PCR System 2700 (Applied Biosystems, Foster City, US) according to the manufacturer's instructions. In brief, the assay was conducted in a final reaction volume of 50 µL containing 10 µL of extracted RNA under conditions that involved initial holds at 50 °C for 30 min and 95 °C for 15 min, followed by 45 cycles of 94 °C for 30 s, 60 °C for 90 s and 72 °C for 60 s. Completed reactions were analysed with the Tape Station platform (Lab901, Edinburgh, UK).

Statistical analysis

Performance parameters of the three RDTs, such as sensitivity and specificity, were calculated using the real-time RT-PCR results as standards. Values were expressed as a 95% confidence interval (CI). Statistical analysis was performed with SPSS statistics software (version 20.0; SPSS, Chicago, IL), using McNemar's test, a chi-squared test or the independent t-test, with $p < 0.05$ considered statistically significant.

Results

Characteristics of enrolled patients

Of the 314 nasopharyngeal specimens, 89 were positive for influenza A, 103 were positive for influenza B and 122 were negative for the influenza virus according to the real-time PCR assay. Of the 89 influenza A-positive specimens, 57 were typed as H3 and 32 specimens were typed as H1N1/2009 using the Seeplex Influenza A/B OneStep Typing Kit (Seegene). Patient age and sex are shown in Table 1. A flow diagram of specimen collection and each test is described in Figure 1.

Comparison of sensitivity and specificity

For the detection of influenza A in terms of sensitivity, Sofia showed 74.2% (95% CI: 63.6–82.6), Veritor showed 73% (95% CI: 62.4–81.6) and Bioline showed 53.9% (95% CI: 43.1–64.4) sensitivity. All three RDTs showed 100% specificity (95% CI: 97.9–100 for each RDT). Statistical differences in sensitivity between the Sofia and Bioline assays were 20.3% ($P < 0.001$) and the same result was noted between the Veritor and Bioline assays as 19.1% ($P < 0.001$). The performance parameters for the three influenza RDTs are summarised in Table 4.

For the detection of influenza A/H1N1/2009, the sensitivities of the Sofia, Veritor and Bioline assays were 84.4, 81.3 and 78.1%, respectively. For influenza A/H3, the sensitivities of the Sofia, Veritor and Bioline assays were 70.2, 66.7 and 40.4%, respectively. The average RT-PCR threshold cycle (Ct) of influenza A A/H1N1/2009 (30.1 ± 22.6) was lower than the average Ct of H3 (34.1 ± 26.0) subtype specimens, which implies that higher viral loads were found in clinical specimens of influenza A A/H1N1/2009 than in specimens of H3. Therefore, the Sofia and Veritor assays show much higher sensitivities in the H3 subtype than the sensitivity of SD Bioline for H3. For the A/H1N1/2009 species, the sensitivity differences between SD Bioline and the other assays were not higher than the sensitivity differences between the systems for the detection of subtype H3. For the detection of influenza B in terms of sensitivity, Sofia showed 82.5% (95% CI: 73.5–89.0), Veritor showed 72.8% (95% CI: 63.0–80.9) and Bioline showed 71.8% (95% CI: 62.0–80.0) sensitivity. All three RDTs showed 100% specificity (95% CI: 97.8–100 for each RDT). The difference in sensitivity between the Sofia and Veritor assays was 9.7% ($P = 0.016$), and the difference in sensitivity between the Sofia and Bioline assays was 10.7% ($P = 0.021$). Veritor showed higher sensitivity than the Bioline assay but the difference between Veritor and Bioline sensitivities was not statistically significant ($P = 0.549$).

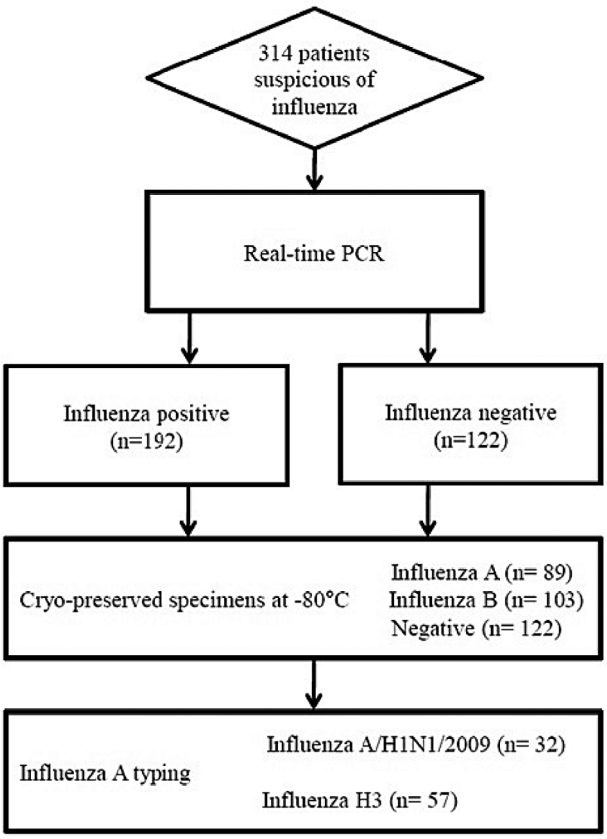

Figure 1. Flow diagram of specimen collection.

Table 4. Performance characteristics of three rapid influenza diagnostic tests for the detection of influenza A/B compared to RT-PCR.

Influenza type	Rapid test	Sensitivity % (*n*, 95% CI)	Specificity % (*n*, 95% CI)
A	Sofia	74.2 (66/89, 63.6~82.6)	100.0 (225/225, 97.9~100)
(*n* = 89)	Veritor	73.0 (65/89, 62.4~81.6)	100.0 (225/225, 97.9~100)
	Bioline	53.9 (48/89, 43.1~64.4)	100.0 (225/225, 97.9~100)
A/H1N1/2009	Sofia	84.4 (27/32, 66.5~94.1)	
(*n* = 32)	Veritor	81.3 (26/32, 63.0~92.1)	
	Bioline	78.1 (25/32, 59.6~90.0)	
H3	Sofia	70.2 (40/57, 56.3~81.2)	
(*n* = 57)	Veritor	66.7 (38/57, 52.8~78.3)	
	Bioline	40.4 (23/57, 27.8~54.2)	
B	Sofia	82.5 (85/103, 73.5~89.0)	100.0 (211/211, 97.8~100)
(*n* = 103)	Veritor	72.8 (75/103, 63.0~80.9)	100.0 (211/211, 97.8~100)
	Bioline	71.8 (74/103, 62.0~80.0)	100.0 (211/211, 97.8~100)

Abbreviations: Sofia, Sofia Influenza A + B Fluorescence Immunoassay; Veritor, BD Veritor™ System Flu A + B; Bioline, SD BIOLINE Influenza Antigen test.

The specificities of all three RDTs were 100% for influenza A and influenza B in negative specimens (both combined or separately). Average RT-PCR threshold cycles (Ct) of influenza A-positive or influenza B-positive specimens for each of the three RDTs are presented in Table 5. Regarding samples that were positive with the Sofia system but negative with the Veritor and Bioline assays, the average RT-PCR Ct (and standard deviation (SD)) was 24.1 (±0.1) for influenza A (*n* = 3) and 35.3 (±1.2) for influenza B (*n* = 6).

Discussion

Influenza virus detection with greater sensitivity and rapidity helps to differentiate other forms of respiratory infection. However, rapid tests for the influenza virus tend to have limitations of detection sensitivity.[6] Many efforts have been made to increase the detection sensitivity of influenza virus detection assays.[3,4,7,8] Recently, digital reader-based assays have been developed to promote detection sensitivity of methods for influenza virus testing.

The Sofia® Influenza A + B Fluorescence Immunoassay and BD Veritor™ System Flu A + B are two examples of FDA cleared,[9] new generation lateral flow digital immunoassays. This study compares two demonstrated digital immunoassays in which the overall sensitivity of the Sofia assay is similar to the results of Lee's study[4] but shows over 10% lower sensitivity in comparison to the results of Dunn's study.[2] In comparing the Sofia and Veritor

Table 5. Real-time RT-PCR threshold cycle (Ct) levels of influenza-positive specimens according to rapid influenza diagnostic test results.

Influenza type	Rapid test	Positive mean Ct (SD)	No.	Negative mean Ct (SD)	No.
A	Sofia	21.7 (3.5)	66	27.3 (5.7)	23
	Veritor	21.7 (3.6)	65	27.1 (5.7)	24
	Bioline	21.3 (3.8)	48	25.4 (5.1)	41
	Sofia only	24.1 (0.1)	3		
	Veritor only	26.1	1		
B	Sofia	30.5 (3.9)	85	34.0 (2.4)	18
	Veritor	30.2 (3.8)	75	33.5 (3.2)	28
	Bioline	30.0 (4.0)	74	33.7 (3.4)	29
	Sofia only	35.3 (1.2)	6		

Abbreviations: Sofia, Sofia Influenza A + B Fluorescence Immunoassay; Veritor, BD Veritor™ System Flu A + B; Bioline, SD BIOLINE Influenza Antigen test.

assays (unlike the findings of Dunn's study), herein, the Sofia system has 10% higher sensitivity for the detection of influenza B.[2] We postulate that the difference might be due to the enrolled patient population and the specimen type. The mean ages of our study population for influenza A and B were 32.9 and 23.3 years, respectively. In contrast, the enrolled patient population in the previous study was a paediatric group of patients under 18 years and fresh nasal washes were used as specimens instead of nasopharyngeal swabs.[2] Many studies report that higher sensitivity is noted with samples from young children than with samples from adults.[10,11] Presumably this is a consequence of higher levels and longer durations of viral shedding in the younger age group.[12] For considering the bias of age distribution, we proceeded the separate analysis of specimens of children (n = 127) in comparison to those of adults (n = 187). Characteristically it showed that the sensitivity of Veritor in adults (55.3%, 95% CI: 40.1–69.8%) was lower than the sensitivity of Veritor in children (73.2%, 95% CI: 59.7–84.2%) in influenza B virus detection. Also, the sensitivity of SD Bioline in adults (63.8%, 95% CI: 48.5–77.3%) was lower than the sensitivity of SD Bioline in children (78.6%, 95% CI: 65.56–88.4%) for the detection of influenza B. For the detection of influenza A, there were no significant sensitivity differences between children and adults (data not shown).

Relative to traditional dipstick-based influenza RDTs, SD Bioline, a new generation lateral flow digital immunoassay, Sofia® Influenza A + B FIA and BD Veritor™ System Flu A + B show much higher sensitivities for the detection of influenza A. The sensitivity differences between traditional RDTs and the digital immunoassays were particularly remarkable in specimens of the H3 subtype of influenza A. In the H3 subtype, observed sensitivity differences were 26.3% (between Veritor and Bioline) to 29.8% (between Sofia and Bioline) between new and traditional RDTs. In contrast, the differences in sensitivity in the detection of subtype A/H1N1/2009 were 3.1% to 6.3% between the two RDT systems. For the detection of influenza A, the SD Bioline and BD Veritor™ System Flu A + B kits showed similar sensitivity. However, the Sofia® Influenza A + B FIA showed higher sensitivities than the Veritor or Bioline assays for the detection of influenza B. This study has some limitations, including that only real-time PCR results were used for influenza confirmation, the mean age of individuals indicated a population primarily composed of young adults and the number of specimens of influenza subtype A/H1N1/2009 was relatively low. However, this study strongly suggests that newly developed digital-based RDTs show higher positive detection rates for the influenza virus than a conventional RDT method.

The Sofia® Influenza A + B FIA and BD Veritor™ System Flu A + B showed higher detection sensitivity for influenza A in comparison to the SD Bioline kit. Particularly in the detection of the H3 subtype of influenza A, the Sofia® Influenza A + B FIA and BD Veritor™ System Flu A + B demonstrated significantly higher sensitivities. Regarding detection of the influenza B virus, the Sofia® Influenza A + B FIA kit showed higher sensitivity than the BD Veritor™ System.

This work represents an advance in biomedical science by verifying that digital-based readout systems for detection of the influenza virus can be applied in clinical settings for more sensitive diagnosis of influenza infections (Table 6).

Table 6. Summary.

What is known about this subject:

- In influenza A, the Sofia digital-based readoutsystem showed 74.2% sensitivity and the Veritor system showed 73% sensitivity, but the Bioline conventional RDT showed 53.9% sensitivity.
- The sensitivities of Sofia, Veritor and Bioline were 84.4, 81.3 and 78.1%, respectively, for influenza A/ H1N1/2009, and 70.2, 66.7 and 40.4%, respectively, for the A/H3 subtype of infl uenza.
- For influenza B, the Sofia system showed 82.5% sensitivity, the Veritor system showed 72.8% sensitivity and Bioline showed 71.8% sensitivity.

What this paper adds:

- In comparison to a conventional rapid diagnostic test, the Sofia and Veritor methods showed higher detection sensitivity for infl uenza A.
- The Sofia and Veritor methods demonstrated remarkably higher sensitivities in the detection of the H3 subtype of infl uenza A.
- The Sofia method showed higher sensitivity for the detection of the influenza B virus than the Veritor method.

Disclosure statement

The authors declare no potential conflicts of interest relevant to this article.

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