Diagnostic Microbiology and Infectious Disease 94 (2019) 227–230

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Virology

Comparison of the Coris Influ A + B K-SeT® and BD Veritor Flu A + B® for rapid detection of influenza viruses in respiratory samples from 3 consecutive flu seasons in Belgium

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1. Introduction

Influenza is a contagious respiratory illness predominantly caused by influenza viruses A and B. Substantial morbidity and mortality can be attributed to seasonal influenza epidemics worldwide. In Europe, the flu seasons of 2014 to 2017 resulted in an excess of 122 deaths per 100,000 people (Vestergaard et al., 2017). Especially vulnerable populations such as pregnant women, the extremes of age, immunocompromised patients, and patients with chronic kidney or heart disease have a high risk of complications, e.g., pneumonia, bacterial superinfection, and death (Centers for Disease Control & Prevention (CDC), 2018).

The rapid laboratory diagnosis of influenza significantly decreases the (mis)use of antibiotics and overuse of laboratory and radiographic testing while prompting infection-control measures, ultimately leading to decreased healthcare costs (Hassan et al., 2014; Petric et al., 2006; Woo et al., 1997). Several methods for influenza detection are currently available such as rapid antigen tests, also known as rapid influenza diagnostic tests (RIDT), and molecular tests. RIDTs have demonstrated a relatively good specificity but lower sensitivity compared to molecular tests (Hurt et al., 2007; Vemula et al., 2016; Weinberg and Walker, 2005). Still, they remain the test of choice in many laboratories due to the short turnaround time (TAT), simplicity in assay procedure, and low cost (Vemula et al., 2016). Among RIDTs, the Veritor Flu A + B® (Becton Dickinson) is a chromatographic immunoassay which has proven to be a reliable and fast test (Dunn et al., 2014; Hassan et al., 2014; Leonardi et al., 2015). Molecular tests are considered as the gold standard, yielding highly specific and sensitive results (Hassan et al., 2014). Newly developed sample-in-result-out molecular systems such as GeneXpert®, Cobas Liat®, or Alere i® are less technically demanding and have shorter TATs than the "old school" RT-PCR assays requiring manual or (semi-)automated extraction and amplification steps. Yet, molecular tests are expensive and are not readily available in every laboratory or outpatient setting (Jonckheere et al., 2015).

This study evaluates the clinical performance and user friendliness of a new commercially available RIDT, the Influ A + B K-SeT® (Coris BioConcept), in comparison with the established Veritor Flu A + B® for the detection of influenza viruses in nasopharyngeal aspirates (NPAs). These NPA specimens were collected during 3 consecutive influenza seasons to challenge the robustness of the assays in detecting different influenza subtypes. Subsequently, the impact on the RIDT performance using fresh versus frozen specimens was evaluated. A commercially available RT-PCR (FTD FLU/HRSV®, Fast Track Diagnostics) was used as reference method. To our knowledge, this is the first study that assesses the above mentioned characteristics of both antigen assays compared to RT-PCR in a diagnostic laboratory setting.

2. Materials and methods

2.1. Clinical samples

NPAs were obtained by nasopharyngeal wash using a syringe with saline water to recover an NPA of approximately 1 mL. Samples were sent to the microbiology laboratory for routine influenza diagnostics using the FTD FLU/HRSV® RT-PCR assay (Fast Track Diagnostics) as part of the clinical workup of patients with influenza-like illness in a tertiary hospital (Antwerp University Hospital) during 3 consecutive flu seasons (2014–2017). One-hundred ninety-eight of these samples were randomly selected to be analyzed by the RIDTs. Samples from flu season 2014–2015 ($n = 57$), 2015–2016 ($n = 63$), and 2016–2017 ($n = 78$) were stored at −80 °C for 2 years, −20 °C for 1 year, and 4 °C, respectively, until analysis. Samples were obtained mostly from children under the age of 6 ($n = 152$, i.e., 77.0%), but also patients older than 65 years ($n = 13$, i.e. 6.6%) were included since the extremes of ages are the most vulnerable patients.

2.2. Influenza detection techniques

2.2.1. Real-time PCR

A commercial kit, FD FLU/HRSV® from Fast-Track Diagnostics, was used as reference test. The kit is capable of detecting RSV and influenza virus A and B simultaneously in multiple types of respiratory specimens, such as NPA, nasal and throat swabs, bronchoalveolar lavage fluid, and sputum. The assay was performed according to the manufacturer's instructions. In short, the RNA was extracted using the NucliSENS® easyMAG® (bioMérieux) semiautomated extractor. An internal

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https://doi.org/10.1016/j.diagmicrobio.2019.01.005
0732-8893/

Table 1
Number of samples tested by RT-PCR and percentages of positive and negative results per season.

Influenza season	No. of tested samples	Influenza A positive	Influenza B positive	Influenza A/B negative
2014–2015	57	32 (56%)	-	25 (44%)
2015–2016	63	7 (11%)	9 (14%)	47 (75%)
2016–2017	78	14 (18%)	-	64 (82%)
Total	198	53 (27%)	9 (4%)	136 (69%)

extraction control (brome mosaic virus) was added to each sample before extraction. After extraction, the RNA extract was transformed to cDNA and amplificated by a real-time one-step PCR on the Lightcycler®480 (Roche).

2.2.2. BD Veritor System for rapid detection of Flu A + B/RSV®

The Veritor Flu A + B/RSV® is an immunochromatographic assay containing murine monoclonal antibodies targeting influenza A or B antigens. Specimens suitable for analysis are NPA, nasopharyngeal swabs, and bronchoalveolar lavage fluid. The assay and quality controls were performed according to the manufacturer's instructions. In short, 300 μL of NPA was added to a prefilled reagent tube containing 100 μL of detergent solution. After vortexing thoroughly, 3 drops of the mixture was dispensed into the sample well of the reagent strip and incubated for 10 min at room temperature. Following incubation, the reagent strip was interpreted by a compact automatic reader which generated a negative, positive, or invalid result after 10 s.

2.2.3. Influ A + B K-SeT® (Coris, Bioconcept)

The Influ A + B K-SeT® is an immunochromatographic assay containing monoclonal antibodies targeting the nucleoprotein antigens of influenza A or B and colloidal gold particles. Specimens suitable for analysis are NPA and nasopharyngeal swabs. The assay and quality controls were performed according to the manufacturer's instructions. In short, 7 drops of extraction buffer were added to 200 μL of NPA followed by thorough vortexing. One hundred microliters of this mixture was added to the sample well of the cassette and incubated for 15 min at room temperature. Following incubation, the reagent strip was interpreted visually by a lab technician, assisted by a second technician in case of doubt.

2.3. Statistical analysis

The results of the 2 antigen tests were divided into the following categories: true positive, true negative, false positive, and false negative with RT-PCR as the gold standard. Subsequently, the performance characteristics, i.e. sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated for the 2 antigen tests and expressed as a 95% confidence interval (CI). Furthermore, test agreement was compared using kappa concordance. To visualize the results of the antigen tests in relation to the cycle threshold (Ct) values of the RT-PCR assay, a whisker-box plot was used and means were compared using Student's *t* test. A *P* value <0.05 was considered statistically significant. Statistical analysis software consisted of Microsoft Office Excel® 2016 software (Microsoft Corporation, USA) and MedCalc® v.17.5.5 (MedCalc Software Ltd., Belgium).

3. Results

Among the 198 nasopharyngeal aspirates, 53 (27%) were positive for influenza A and 9 (5%) for influenza B by FTD FLU/HRSV® RT-PCR (Table 1), resulting in an overall influenza positivity rate of 32%. The median age in the population positive for influenza A or B was 2 years (1–5 years 95% CI). The proportion of influenza-positive patients per age group was as follows: 26% of children under the age of 6, 45% of patients between 6 and 65 years of age, and 38% of patients older than 65 years. There were 9 invalid RIDT-results: 6 for Influ A + B K-Set® (3 PCR positive, 3 PCR negative) and 3 for Veritor Flu A + B® (1 PCR positive, 2 PCR negative). Hence, the number of eligible samples for data analysis was 192 for Influ A + B K-SeT® and 195 for Veritor Flu A + B®. The overall performance characteristics for both RIDTs compared to RT-PCR are depicted in Table 2. Of the PCR-positive samples ($n = 62$), the Influ A + B K-SeT® detected 43/51 (84.3%) influenza A and 5/8 (62.5%) influenza B, while the Veritor Flu A + B® detected 47/52 (90.4%) influenza A and 7/9 (77.8%) influenza B, resulting in overall sensitivities of 81.4% and 88.5% for Influ A + B K-SeT® and Veritor Flu A + B®, respectively. Influ A + B K-SeT® missed 8 influenza A and 3 influenza B positive samples (NPV 92.3%) in contrast to Veritor Flu A + B® which missed 5 influenza A and 2 influenza B positive samples (NPV 94.9%). The Influ A + B K-SeT® false negatives had RT-PCR Ct values ranging from 22.66 to 28.92, which were not significantly different from the Ct values of the Veritor Flu A + B® false negatives ranging from 25.89 to 28.92 ($P = 0.2$). For both RIDTs, true-positive samples had a significantly lower Ct value compared to false-negative samples as shown in Fig. 1. Influ A + B K-SeT® generated 2 and Veritor Flu A + B® 3 false-positive influenza A results, resulting in specificities of 98.5% and 97.8% and PPVs of 96.0% and 94.7% respectively. Concordantly, both RIDTs achieved very good interrater agreement with RT-PCR as demonstrated by a kappa value of 0.83 (0.75–0.92 95% CI) for Influ A + B K-SeT® and 0.88 (0.81–0.95 95% CI) for Veritor Flu A + B®. In spite of comparable performance characteristics, there were 8 discrepant results between the Influ A + B K-SeT® and the Veritor Flu A + B®. Seven samples were positive with Veritor Flu A + B® but negative with Influ A + B K-SeT, of which 2 were negative and 5 positive by RT-PCR. These RIDT discordant true-positive samples (mean Ct 24.57, 22.31–26.83 95% CI) did not show a significant difference ($P = 0.8$) in Ct values compared to the RIDT concordant true positives (mean Ct 22.83, 22.04–23.62 95% CI). One sample

Table 2
Performance characteristics of the Veritor Flu A + B® and Influ A + B K-SeT® with reference RT-PCR.

	Influenza A		Influenza B	
	Influ A + B K-SeT® ($n = 192$)	Veritor Flu A + B® ($n = 195$)	Influ A + B K-SeT® ($n = 192$)	Veritor Flu A + B® ($n = 195$)
True positives	43	47	5	7
False negatives	8	5	3	2
True negatives	139	140	184	186
False positives	2	3	0	0
Sensitivity	84.3	90.4	62.5	77.8
(% [95% CI])	(71.4–93.0)	(79.0–96.8)	(24.5–91.5)	(40.0–97.2)
Specificity	98.6	97.9	100.0	100.0
(% [95% CI])	(95.0–99.8)	(94.0–99.6)	(98.0–100.0)	(98.0–100.0)
PPV	95.6	94.0	100.0	100.0
(% [95% CI])	(84.4–98.8)	(83.6–98.0)	(46.3–100.0)	(56.1–100.0)
NPV	94.6	96.6	98.4	98.9
(% [95% CI])	(90.2–97.0)	(92.4–98.5)	(96.2–99.3)	(96.5–99.7)

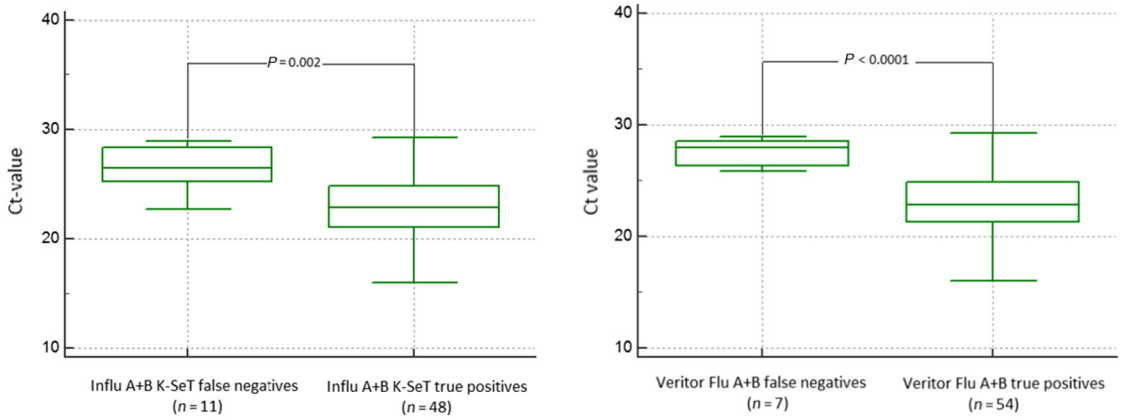

Fig. 1. Whisker-box plots comparing PCR Ct values of Influ A + B K-SeT® true-positive and false-negative samples (left panel) and Veritor Flu A + B® true-positive and false-negative samples (right panel).

was detected positive by Influ A + B K-SeT® but not by Veritor Flu A + B® and was confirmed by RT-PCR as positive (Ct value 25.89).

Some variables may have an effect on the robustness of the assays studied. The majority of the samples in this study were kept frozen until analysis, which might have affected the performance characteristics. Table 3 shows the number of correct results (true positives + true negatives) for the 2 storage conditions compared to RT-PCR for both assays. There was no significant difference between fresh and frozen samples or between the 2 assays in terms of correct results. Also, the age of the study population did not have a significant influence on the performance of either assay. Twenty-five samples of adult patients (>18 years old) were all correctly classified by Veritor Flu A + B® compared to RT-PCR. Twenty-three adult samples were tested with Influ A + B K-SeT®, of which only 2 samples showed false-negative results compared to RT-PCR. The cause of the discordancy was most likely the flocculent condition of the samples as opposed to the patients' age (both >65 years old).

Regarding user friendliness, the processing time and ultimately TAT are important. The overall processing time of the Influ A + B K-SeT® and Veritor Flu A + B® was 17 and 12 min for a single specimen, respectively, with a hands-on time for both around 2 min. To assure the shortest TAT, unambiguously positive or negative results are desired as opposed to invalid results. The sample's condition is pivotal to obtain reliable results: ideally, it is clear and easily aspirated. There were 9 invalid results: 3 with the Veritor Flu A + B® and 6 with the Influ A + B K-SeT®. Revision of these samples consistently showed viscous and/or flocculent NPAs. In compliance with this observation, samples which were clear or even hemolytic or cloudy but easy to aspirate had no invalid results in this study.

4. Discussion

On-site diagnosis of influenza by point-of-care (POC) tests helps to decrease prescription of antimicrobials and requests for blood cultures and chest radiography, ultimately leading to reduced healthcare costs (Bonner et al., 2003). Rapid antigen tests for influenza are very useful as a POC test due to their short TATs (15–30 min), low cost, and ease of use (Hassan et al., 2014), although they do not approach the diagnostic accuracy of molecular methods.

In this study, the Influ A + B K-SeT® (Coris, Bioconcept) and Veritor Flu A + B® (BD) were compared with FTD FLU/HRSV® (Fast-Track Diagnostics) for detecting influenza A and B viruses in clinical samples. The overall sensitivity and negative predictive value of the Veritor® system were higher than the Influ A + B K-SeT®. The specificity and positive predictive value were high for both assays, with a small advantage for the Influ A + B K-SeT®. These are critical performance characteristics affecting the patient's management. It is important to identify the infected patients in need of antiviral therapy and infection-control measures while restricting their use of antimicrobials and preventing unnecessary hospitalization. Our results for Veritor Flu A + B® are comparable to the claim of the manufacturer and other previously published studies, who reported overall sensitivities ranging from 70.7 to 98.1% and specificities ranging from 94.0 to 100.0% compared to RT-PCR (Dunn et al., 2014; Hassan et al., 2014; Leonardi et al., 2015; Mese et al., 2016; Nam et al., 2014; Ryu et al., 2018). Studies using nasopharyngeal swabs found lower sensitivities (median 82.4%) than our study which used solely NPA (Leonardi et al., 2015; Mese et al., 2016; Nam et al., 2014; Reynders et al., 2012; Ryu et al., 2018). No studies are available to evaluate the performance characteristics that we obtained for Influ A + B K-SeT®, which were lower than those claimed by the manufacturer (Coris BioConcept), i.e., 100% for all parameters (Coris BioConcept, Gembloux, Belgium, 2016). It is important to note that they used immunofluorescence as reference method. Yet, several studies showed that PCR assays were significantly more sensitive than immunofluorescent assays for diagnosis of viral respiratory infections (Kuypers et al., 2006).

Regarding the robustness of both RIDTs for the different influenza subtypes and lineages, no definite conclusion can be made. According to the Belgian national reference center for influenza, the flu seasons 2014–2015 and 2016–2017 were characterized by a predominance of influenza A (mainly subtype H3N2) and little influenza B (mainly Yamagata lineage). Flu season 2015–2016 was marked by an equal prevalence of influenza A (mainly subtype pdmH1N1) and influenza B (mainly Victoria lineage) (WIV-ISP, 2018). Table 1 demonstrates the distribution of samples over the 3 flu seasons and their influenza status based on the FTD FLU/HRSV® RT-PCR reference test. Good performance characteristics were obtained in this study spanning the mentioned flu seasons. This mirrors the reality of receiving different influenza strains, yet for these study samples, confirmatory typing was not obtained. The majority of samples have been frozen prior to analysis though fresh samples are recommended by the manufacturers to assure the best performance. We compared the correct results of both assays obtained with frozen versus fresh samples and observed no difference. We conclude that 1 freeze–thaw cycle does not affect the performance of both RIDTs. Age on the other hand might affect the performance of RIDTs as it has been shown to be better in children compared to adults, potentially due to higher viral loads and longer viral shedding in children (Cruz et al., 2010). According to our findings, age does not seem to have a significant influence on the performance of either assay. This has to be interpreted cautiously given the sample size. Discordances in our study were most likely explained by the flocculent condition of the samples as opposed to the patients' age. Both assays have difficulties analyzing viscous or flocculent samples, leading to invalid results due to absence of a reaction at the quality control position. A possible solution would be to dilute the sample to obtain a sufficiently liquid sample which is easy to aspirate and which can distribute itself properly along

Table 3
Agreement among testing of fresh versus frozen specimens.

	Correct results / interpretable results (%) compared to RT-PCR	
	Fresh	Frozen
Influ A + B K-SeT®	70 / 76 (92%)	109 / 116 (94%)
Veritor Flu A + B®	72 / 76 (95%)	113 / 119 (95%)

the test strip. The resulting performance is uncertain as the sensitivity can be compromised by decreasing the viral load.

Other criteria for RIDTs such as the user friendliness and TAT are also of importance, particularly considering the use in an outpatient setting. The Veritor Flu A + B® performs better on these aspects than the Influ A + B K-SeT®, being 5 min faster and easy to interpret when using the digital reader, which eliminates subjective, visual interpretation. However, in any case, an inspection of the test strip is needed to check the absence of abnormalities that might interfere with correct reading (Becton, Dickinson and Company, Maryland, USA, 2016). By contrast, the Influ A + B K-SeT® requires interpretation by the test operator which can be challenging especially when test lines are very faint. According to the manufacturer's instruction, any (weak) red to purple line at the test line position should be considered a positive result. The kit insert warns not to mistake a faint shadow, which can occur as result of the drying process, as a positive result (Becton, Dickinson and Company, Maryland, USA, 2016). These interpretation rules are prone to interindividual variability and misdiagnosis (Jonckheere et al., 2015). In our study, each reagent strip was judged by the same laboratory technician, assisted by a second technician in case of doubt. In settings where this immunochromatographic assay would be used by multiple test operators, more variation might be expected.

Our study indicates that RIDTs have a good performance in comparison to RT-PCR and show robustness regarding their results for several subtypes of influenza type A. Nonetheless, molecular POC assays are emerging as a worthy competitor, providing high sensitivity and multiple pathogen detection. The most pronounced disadvantage is the cost of such assays. RIDTs on the other hand are very easy to use, quick, and more affordable. In settings where molecular tests are not readily available, an RIDT can be of great value despite its lower sensitivity (Leonardi et al., 2015).

5. Conclusion

In summary, both RIDTs performed well in detecting influenza virus A and B in nasopharyngeal aspirates compared to RT-PCR as reference method, with a higher sensitivity for the Veritor Flu A + B® test. Visual result interpretation of the Influ A + B K-SeT® requires trained lab technicians, while the digital reader of the Veritor® system minimizes operator errors. To our knowledge, this is the first study assessing the performance characteristics, robustness, and user friendliness of the assays mentioned in a diagnostic laboratory setting.

Acknowledgments

Influ A + B K-SeT® tests were kindly provided by Coris Bioconcept.

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